Review paper
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VITAMIN B3 DIETARY INTAKE AND ITS ROLE IN AGING

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Abstract

Organism aging is a process of time and maturation culminating in senescence and death. The molecular details that define and determine aging have been intensely investigated in last decade. The aim of this review is to improve the dietary intake of vitamin B3 (niacin) as an agent that is critical for modulating cellular metabolism, mitochondrial plasticity, longevity, and for influencing cellular life span.

Bibliographical searches were performed in available studies and reports using the following terms: "vitamin B3", "niacin and aging", "mitochondria and aging", "nicotinamide" and "age related diseases".

Nicotinamide, the amide form of niacin (vitamin B3), is the precursor for the coenzyme beta-nicotinamide adenine dinucleotide - NAD(+), and plays a significant role during the enhancement of cell survival as well as cell longevity. Normal intake of Vitamin B3 obtained through diet with: fishes, turkey, avocado, mushrooms and other products, raise the capacity of nicotinamide to govern not only intrinsic cellular integrity, but also extrinsic cellular inflammation rests. This process is proven by modulation of a host of cellular targets that involve mitochondrial membrane potential, poly (ADP-ribose) polymerase (PARP), protein kinase B (Akt), caspases and microglial activation.

Given the wide array of cellular functions regulated by nicotinamide, it becomes critical to elucidate the cellular pathways controlled by this agent. Further insight into the spectrum of cellular processes modulated by nicotinamide should open the space for the future development of new therapeutic strategies for a spectrum of disorders that may involve aging, and age related diseases.

***Key words**: Aging, Diet, Vitamin B3, Nicotinamide, Mitochondria.*

1. Introduction

Organism aging is a process of time and maturation culminating in senescence and death. The molecular details that define and determine aging have been intensely investigated [1]. It has become appreciated that the process is partly an accumulation of random yet inevitable changes, but it can be strongly affected by genes that alter lifespan. Vitamin B3 or niacin is a precursor of nicotinamide dinucleotide NAD+, the substrate for the activity of DNA repair enzyme PARP-1 and, consequently, may contribute to maintaining genomic stability.

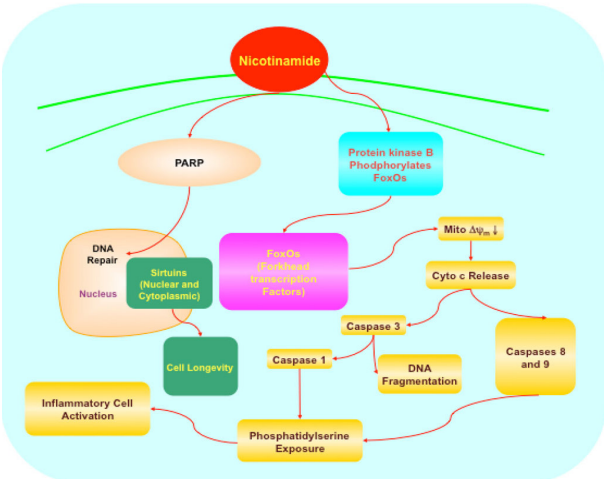

Figure 1. Nicotinamide relies upon novel cellular pathways to impact cell survival, longevity, and immune system function. Nicotinamide controls apoptotic early phosphatidylserine exposure, DNA repair and degradation, cell longevity, and immune cell activation through multiple pathways that involve modulation of sirtuin activity, protein kinase B (Akt), poly (ADP-ribose) polymerase (PARP), fork head transcription factors, mitochondrial membrane potential ($\Delta\Psi_m$), cytochrome c, (Cyto-c), and caspases 1,3, 8, and 9. These pathways can then regulate the onset of early apoptotic injury with phosphatidylserine exposure, late injury with nuclear DNA degradation, and inflammatory cell activation.

The metabolism of NAD(+) plays important roles in the random patterns of aging, and also in the more programmatic aspects. The derivatives of NAD(+), such as reduced and oxidized forms of NAD(P)(+), play important roles in maintaining and regulating cellular redox state, Ca^{2+} stores, DNA damage and repair, stress responses, cell cycle timing and lipid and energy metabolism. NAD(+) is also a substrate for signaling enzymes like the sirtuins and poly-ADP-ribosyl polymerases, members of a broad family of protein deacetylases and ADP-ribosyl transferases that regulate fundamental cellular processes such as transcription, recombination, cell division, proliferation, genome maintenance, apoptosis, stress resistance and senescence [2]. NAD(+)-dependent enzymes are increasingly appreciated to regulate the timing of changes that lead to aging phenotypes. We consider how metabolism, specifically connected with vitamin B3 and the nicotinamide adenine dinucleotides and their derivatives, occupies a central place in the aging processes of mammals. The main pathways in the metabolism of nicotinamide are shown in Figure 1.

2. Mitochondrial mutations and aging

The metabolism of niacin is tightly connected with the condition and normal function of the specific cellular organelles - mitochondria. Mitochondria play essential and diverse roles in the physiology of eukaryotic cells. These structures are not only indispensable for ATP production and participate in numerous intermediate metabolic reactions, but also play a central role in calcium homeostasis, apoptosis, cell signaling, and differentiation. Impairment of mitochondrial functions has been implicated in a wide variety of human pathologies including cancer and age-related diseases such as type II diabetes mellitus (DM II), Alzheimer's disease, degenerative arthritis, ischemic heart disease, and age-related macular degeneration [3, 4].

Numerous papers have analyzed the increased occurrence of mitochondrial mutations and deletions in aging cells in various organisms [5 - 7]. The fact that older cells in various tissues, especially in postmitotic ones, accumulate both point mutations and deletions in mitochondrial DNA is undisputed, but there have been a number of problems interpreting these results. First, relatively high percentages of mutations are known to be required to affect the respiratory chain, on the basis of data from patients with mitochondrial diseases. Second, the correlation of point mutations and deletions with aging is not proof of causality - only of coexistence. Another problem which has been controversial is what the effects of the mutations are - do they cause a vicious cycle of reactive oxygen species (ROS) release, as was postulated by Harman [8], with more and more new mutations leading inevitably to cell death?

In the last 10 years two models have resolved some, but not all of the problems which have been raised in studies of aging and mitochondria. The first was the mutator mouse, obtained independently by two groups [9, 10] with a mutated mitochondrial DNA polymerase which led to accumulation of large numbers of mutations in the mitochondrial DNA. The mice showed symptoms of premature aging and, as the mutations came before the aging this was proof of causality. There are still, however, some problems with the interpretation of the results obtained with these models. Why are heterozygous mice which accumulate a high number of mutations healthy? Are deleted mtDNA molecules the cause of aging? Do they occur? The different techniques used and different results obtained by the two groups make it difficult to analyze what exactly is happening during the aging process, but some things do appear to be clear - there are numerous point mutations, they lead to cell death and eventually aging, and all this takes place without any excessive production of reactive oxygen species [11 - 13].

The second result was perhaps less spectacular than those obtained with the mutator mouse, but is very important for solving the problem of whether and how low levels of mitochondrial DNA mutations can affect the functioning of cells? Dufour *et al*., [14] found that a mitochondrial respiratory chain deficiency in neurons which was caused by a nuclear mutations when present in only 20% of the mitochondria caused degeneration of adjacent neurons. This points to a solution of the problem that the levels of mutations found in aging tissues are too low. Thus, mitochondrial mutations are now generally believed to be involved in the aging process, probably through the role of sirtuin proteins in the cells.

2.2 The sirtuin proteins

Originally characterized in yeast as regulators of life span [15], the sirtuins (Silent Information Regulator) are an evolutionarily conserved family of proteins that appear to exert a wide range of biological functions [16]. Based on sequence similarity, sirtuins can be grouped into different classes. Mammals have seven sirtuins, Sirt1 - 7. Among them, only Class I sirtuins (Sirt 1 - 3) have robust deacetylase activity. Sirt 4 - 7 have either no detectable or very weak deacetylase activity. Sirt1 appears to be the closest mammalian homolog to yeast Sirt 2, the first member of the sirtuins linked to aging. Because of this homology, initial studies of mammalian sirtuins focused predominantly on the biology of Sirt1. Insights from these studies have implicated Sirt1 in the regulation of a variety of metabolic phenotypes including: insulin secretion [17], lipid mobilization from adipocytes [18], and regulation of glucose tolerance [19].

The ability of sirtuins to influence metabolism and potentially life span is believed to revolve around the ability of sirtuin family members to function as protein deacetylases. In addition to this enzymatic function, Sirt 4 can further act to ADP ribosylate target proteins. Unlike other protein deacetylases, sirtuins require nicotinamide adenine dinucleotide (NAD) as a cofactor in the deacetylation reaction [16]. The recent studies indicate that the nuclear Sirt1 is an important regulator of mitochondrial function. Comparative analysis of total liver mitochondrial protein acetylation following distinct genetic knockout of each of the three mitochondrial-enriched sirtuins-Sirt3, Sirt4, and Sirt5-showed that Sirt3 is the major mitochondrial deacetylase [20]. At the same time, the dynamic flux in mitochondrial protein acetylation in response to changes in caloric load as illustrated by feeding and fasting, caloric restriction, and caloric excess [21, 22] suggest that, as is the case with Sirt1, Sirt3 may possess a nutrient-sensing regulatory role governing mitochondrial protein function.

The mitochondrial sirtuins also appear to play an important role in the control of reactive oxygen species. This regulatory role may be particularly relevant to modulating the development of age-associated degenerative conditions [23]. At the direct substrate level, the reactive oxygen species scavenging enzyme MnSOD is activated by Sirt3, and numerous lysine residues have been implicated in mediating this induction of enzyme activity [24].

2.3 Food that contain vitamin B3

The vitamin B3 we get from food includes preformed niacin and the amino acid tryptophan, which can be converted to niacin in the body. Niacin equivalent is the term used to refer to either 1 mg of niacin or to 60 mg of tryptophan (it takes 60 mg of tryptophan to make 1 mg of niacin). Most proteins contain tryptophan. In the average protein-rich American diet, tryptophan provides about 60 percent of the niacin we need. If a diet is adequate in protein, then it will surely supply enough niacin equivalents from both sources to meet daily needs. The best sources of niacin are foods with a high protein content, such as meat, eggs, and peanuts. Other good sources of vitamin B3 equivalents, such as milk, actually provide more tryptophan than niacin [25]. Mushrooms and greens are good vegetable sources. Vitamin B3 is also added to enriched breads and cereals to replace that lost during processing. The list of food rich with Vitamin B3 is not so long and the listed articles are of benefit for normal cell activity that imply anti-age properties. The best of all are fishes, especially tuna - 100 g of tuna contains 22.1 mg niacin. The list is followed by lamb liver (16.7 mg), turkey (14.8 mg niacin), peanuts (13.8 mg), pork (10.8 mg), beef (9.7 mg), sunflower seeds (8.3 mg), mushrooms (6.3 mg), green peas (2.1 mg), and avocado (with 1.7 mg niacin in 100 g). The list of anti-ageing food runs with walnuts, some vegetables, dark chocolate, berries, red wine, green tea, melons and watermelons, beans, turmeric, spirulina, goji berries, pomegranates and many more with much lower level of niacin, but with higher concentration of some essential amino acids [26].

3. Conclusions

- The body absolutely needs to have an adequate supply of niacin or niacinamide available to make the amounts of NAD and NADP required for health. Further, this must come from dietary sources, foods or supplements.

- The research literature related to therapeutic use of niacin/niacinamide is at first confusing expressing different viewpoints that have emerged during different periods of time and representing different ways of looking at the effects of substance. Some articles cite reasons why large doses of niacin may promote longevity, and other articles cite reasons why such use may shorten life.

- For about 40 years large doses of niacin have been used for several therapeutic purposes. Many physicians currently prescribe large doses of niacin for lipid control and other purposes. Mild benefits seem to exist in some areas like raising HDL cholesterol, and thus, preventing diseases of heart and blood vessels. The long-term consequences of repeatedly taking large doses are unknown.

- Large scale niacin dosage profoundly affects multiple genes through multiple pathways producing both wanted and unwanted results. While many researchers are excited by the possibilities of niacin-related therapies for a variety of conditions, the one thing they agree on is a need for further understanding of the pathways involved.

- The sirtuin-related pathways involving the niacin metabolites NAD and NADP are among those related to niacin most intensely studied in recent years. Large doses of niacin/niacinamide inhibit the expression of SIRT1 and therefore prevent the health and longevity benefits associated with expression of SIRT1.

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