An important molecule for life: The cellular energy sensor 'NAD+'.

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Abstract

Nicotinamide Adenine Dinucleotide (NAD+) has essential functions in metabolism. NAD+ is an oxidizing agent and it accepts electrons from other molecules and becomes reduced. The balance between the oxidized and reduced forms of NAD is called the NAD+/NADH ratio. In metabolism, NAD+ is involved in redox reactions, carrying electrons from one reaction to another, therefore, found in two forms in cells. This ratio is an important component of what is called the redox state of a cell, a measurement that reflects both the metabolic activities and the health of cells. NAD+ is also involved in fundamental metabolic processes including glycolysis, the citric acid cycle, and mitochondrial oxidative phosphorylation leading to energy production. NAD+ has been shown to be the key substrate for poly(ADP-ribosyl)polymerases, NAD+ glycohydrolases, and histone deacetylases known as sirtuins. These enzymes have been termed 'NAD+' consumers, and are involved in modulation of DNA repair, maintenance of intracellular calcium homeostasis and immunological roles, and epigenetically modulated gene expression. In conclusion, researchers focus on the metabolism of NAD+ is used by the body as area of intense researches on unravelling the secrets of our cellular 'energy sensor' NAD+ for promoting healthy ageing. Therefore, researches in the last two decades have shown that NAD+ is more than a mere regulator of metabolism, but rather may play a key role in the ageing process.

Keywords: Anti-ageing, Cellular Energy, Coenzyme, Metabolism, NAD+.

Introduction

Numerous studies have shown that there exists and inverse relationship between the metabolic rate of an organism and its maximum life span. This is led to the hypothesis that ageing is a process caused by damage to tissue and cells due to an imbalance between the production of reactive oxygen species, and the body's natural endogenous antioxidant defense mechanisms. The researchers focus on the metabolism of Nicotinamide Adenine Dinucleotide (NAD+) is used by the body as area of intense researches on unraveling the secrets of our cellular 'energy sensor' NAD+ for promoting healthy ageing [1-4].

NAD+ is an important cofactor to metabolism in all living cells. In metabolism, NAD+ is involved in redox reactions, carrying electrons from one reaction to another, therefore, found in two forms in cells. NAD+ is an oxidizing agent and it accepts electrons from other molecules and becomes reduced. The balance between the oxidized and reduced forms of NAD is called the NAD+/NADH ratio. This ratio is an important component of what is called the redox state of a cell, a measurement that reflects both the metabolic activities and the health of cells [1-4].

NAD+ has essential functions in metabolism. NAD+ and its related derivatives are major coenzymes in over 400 enzymatic reactions, such as oxidoreductases and dehydrogenases. We need NAD+ for the enzyme, alcohol dehydrogenases to breakdown alcohol in the liver. NAD+ is also involved in fundamental metabolic processes including glycolysis, the citric acid cycle, and mitochondrial oxidative phosphorylation leading to energy production. However, research in the last two decades has shown that NAD+ is more than a mere regulator of metabolism, but rather may play a key role in the ageing process [1-5].

NAD+ deficiency was a major epidemic in the last century. Pellagra is a syndrome cause by a diet seriously deficient in synthetic precursors for the essential pyridine nucleotide NAD+, namely niacin and tryptophan. This lethal disorder can develop within 60 days of maintaining a deficient diet due to the absence of free stores of Nicotinic Acid (NA) or nicotinamide (NAM). Individuals diagnosed with pellagra-induced dementia can be successfully treated in the early stages of the disease. However, untreated pellagra results in irreversible neurological damage and eventually death. This is due to primarily to reduced NAD+ production and availability as NAD+ [1-5].

NAD+ has been shown to be the key substrate for poly(ADP-ribosyl)polymerases, NAD+ glycohydrolases, and histone deacetylases known as sirtuins. These enzymes have been termed 'NAD+' consumers, and are involved in modulation of

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DNA repair, maintenance of intracellular calcium homeostasis and immunological roles, and epigenetically modulated gene expression. Gene silencing by sirtuins has been shown to extend lifespan in yeast and small mammals [1-5].

Poly(ADP-ribose) polymerase (PARP) is like a nuclear chain reaction. DNA strand breaks are known to occur in response to free radicals, ultraviolet light or alkylating chemicals which activate the enzyme PARP. The ADP-ribosylation of PARP triggers the recruitment of key proteins that stimulates the repair of the DNA damage in less than 15 s. Importantly, in order for PARP to carry out its ADP-ribosylating function it uses the ADP ribose moiety of NAD+ for its supply. Therefore, PARP breaks down NAD+ to NAM and an ADP-ribosyl product. That's a lot of NAD+ broken down in a very short time. Under physiological conditions, PARP activation can lead to DNA repair and cell survival, and NAD+ regeneration through NAD+ salvage from nicotinamide. However, hyper activation of PARP during pathology can lead to NAD and ATP depletion, and cell death via energy restriction. A significant decrease in intracellular NAD+ has been reported in the brain and other organs as a result of DNA strand breaks and PARP activation following exposure to hydrogen peroxide, nitric oxide, HIV infection, or during inflammation. Inhibition of PARP activity, following oxidant injury has been shown to preserve NAD+ and ATP levels preventing cell lysis, although damage to the DNA is probably not prevented. Elevated levels of free radicals, oxidants, and excitotoxins have been reported in inflammatory mediated diseases of the brain, and in some cases, DNA damage has been demonstrated. This suggests that NAD+ depletion through PARP activation may play a role in ageing and age-related diseases [3-6].

Sirtuins are NAD+ dependent deacetylases that regulate a wide array of proteins involved in metabolism and cell survival. At least 7 sirtuins have been identified in mammalian cells. Sirt1 is located in the nucleus where it is involved in the deacetylation of tumor suppressor protein, p53 and other transcription factors, providing protection against cellular stress and enhancing cell survival. Sirt2 is found in the cytoplasm where it is involved in maintenance of cytoskeletal structure and cell division and therefore acts as a mitotic checkpoint. Sirt3, Sirt4, and Sirt5 are mitochondrial sirtuins and are involved in mediating optimal mitochondrial function. Sirt6, another nuclear sirtuin is involved in DNA repair, although the exact mechanism remains unclear. Sirt7 is found in the nucleosome, which is inside the nucleus where it is involved in RNA transcription. The crucial processes would not be possible without optimal sirtuin activity and levels of the essential substrate, NAD+. The acetylation/deactylation status of sirtuins serves as an ageing/longevity. For example, increased acetylation status due to reduced sirtuin activity can direct cells towards an anti-oxidative phosphorylation state leading to cellular senescence and apoptosis. However, increased deactylation by sirtuins can enhance cellular bioenergetics, promote DNA repair, and extend lifespan and healthspan [3-8].

The conceptual translation so to speak is supported by data indicating that intracellular NAD+ levels decline in catabolic tissue during ageing process parallel to increased oxidative stress and reduced antioxidant levels. Endogenous concentration of the NAD+ metabolome can vary within specific wide ranges depending on age, and exposure to environmental and lifestyle factors. Although it has been argued by many that NAD+ is an intracellular molecule, NAD is exported from the cell in minimal amounts rather than being directly synthesized. NAD is rapidly metabolized and its products are also biologically active, and NAD interacts directly with receptors and then is catabolized rapidly to inactivate its action. NAD is a ligand for various subtypes of purinergic P2 receptors. NAD may also regulate insulin receptor signalling. I recently showed that extracellular NAD+ levels also decline as a function of ageing. There is a reduction in the NAD+/NADH ratio indicative of impaired redox function. There also is an increase in NAD/ADPR ratio confirming that aDP-ribosylation is increased with age. And also there is a reduction in the NAD+/NAM ratio, suggesting that while NAM, a precursor for NAD+ is increased with age, NAD salvage from NAM is impaired, possibly due to reduced enzyme activity [4-8].

Several NAD+ precursors have been identified in our natural diet. These include the amino acid tryptophan, and three forms of vitamin B3 - NA, NAM and Nicotinamide Riboside (NR). Tryptophan catabolism *via* the kynurenine pathway can lead to de novo NAD+ synthesis. NA and NR are precursors that are found in the basic food chain. NA is produced by plants, while NR is present in milk. NAM is formed as a by-product of enzymatic degradation of NAD+, and is the main form of vitamin B3 that can be absorbed from animal-based food. The provision of these vitamins to NAD+ is aided by several factors, including the gut microbiome. Biosynthetic genes are also regulated by circadian rhythms. NR produces greater increases in hepatic NAD+ metabolism than Nam or NA with distinctive kinetics. This provides more evidence for the importance of NR as a favourable NAD+ precursor [4-9].

Alzheimer's Disease (AD) is the most common form of dementia, and there is no cure. DNA repair activity is deficient in AD patient brains, especially DNA polymerase β (Polβ), a key protein in DNA base excision. NAD+ is a cellular metabolite critical for mitochondrial health and biogenesis, stem cell self-renewal, and neuronal stress resistance [4-6].

Myocardial metabolic impairment is a major feature in chronic heart failure. As the major coenzyme in fuel oxidation and oxidative phosphorylation and a substrate for enzymes signaling energy stress and oxidative stress response, NAD+ is emerging as a metabolic target in a number of diseases including heart failure. NR may also protect against ethanol induced liver injuries. Ethanol significantly decreased the expression and activity of hepatic SirT1 and induced abnormal expression of enzymes of lipid metabolism in mice [4-9].

The feasibility of other non-pharmacological strategies to increase NAD+ such as following a low protein ketogenic diet to enhance the NAD+: NADH redox ratio, and/or intermittent fasting or regular exercise to boost caloric restriction should also be addressed. When rats were exposed to a ketogenic diet, significant increases in hippocampal NAD+/NADH ratio.

Based on diverse published literature and these initial data we suggest that increased NAD during ketolytic metabolism may be a primary mechanism behind the beneficial effects of this metabolic therapy in a variety of brain disorders and in promoting health and longevity [4-10].

Supplementation with NR has been shown to increase stem cell number in aged mice, and improving mitochondrial function. But reduced expression of cell senescence and increased apoptosis markers has been reported, suggesting that alteration of the redox potential of NAD+ may lead to a non-optimal reductive state [5-12].

NAD+ overload can increase SIRT1 activity which can stimulate cell survival and proliferation, and increased NAD+/NADH ratio can switch the acetylation status of the tumor suppressor protein p53 towards deacetylation, thus preventing apoptotic cell death. Extracellular NAD+ has been shown to induce apoptosis of naive T cells and incubation of cells with NAD+ can stimulate cellular death by activation of P2X7 receptor on cell the surface. This may increase susceptibility to autoimmune disease [6-12].

Conclusion

NAD+ has been shown to play a unique role in DNA repair and epigenetic control through protein deacetylation. While NAD+ therapy alone is not the mythical 'elixir of life', its foundational role in cellular energetics, nuclear signalling and viability suggest it just may be a key ingredient. Newer more convenient ways to more effectively deliver NAD+ in humans is needed. Being able to quantify NAD+ and NAD-related metabolites should be conducted first prior to using NAD+ therapy or NAD+ precursors to increase your NAD+ levels.

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