How is NAD+ Related to an Anti-Aging Effect on the Human Body?

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Introduction

Muscle tissue is one of the most abundant tissues in the human body and is responsible for creating locomotion between harmonized cellular contractions (Chubanava & Treebak, 2023). Some studies have deduced that the presence of abundant NAD^+ (nicotinamide adenine dinucleotide) can create aging prevention in muscle fitness, especially when coupled with an active lifestyle (Chubanava & Treebak, 2023). Within this paper is the evidence to support the fact that NAD^+ is related to aging effects, how NAD+ is generated, and how we can prevent aging using this molecule.

NAD^+ is a molecule used to transport electrons throughout cell homeostasis processes and is used in a network of essential cellular cycles like many metabolic pathways, DNA repair, and cellular signaling (Aman et al., 2018). The molecule can be found in different forms, namely NADH, NADP+, and NADPH (Covarrubias et al., 2020). Originally, NAD^+ binds to hydrogen ions to form NADH, the reduced version of NAD^+(Covarrubias et al., 2020). This molecule then transports the ions throughout the cell and eventually becomes oxidized to form NAD^+ and a hydrogen ion (Covarrubias et al., 2020). NAD+ can also be phosphorylated to form NADP+, which can be reduced to form NADPH, used in anabolic pathways as a buffer against oxidative stress (Covarrubias et al., 2020). In turn, each form plays an important role in the regular function and maintenance of our bodies.

How is NAD+ created?

In the muscles, NAD+ is generated from the nicotinamide (NAM) salvage pathway from a few different precursors (Covarrubias et al., 2020). NAM can be used as a precursor, but NAM, nicotinamide riboside (NR) or nicotinamide mononucleotide (NMN) can also be used as a precursor (Aman et al., 2018). These precursors can be found in a variety of foods like meat, dairy, and fruits and vegetables (Covarrubias et al., 2020). The precursors are imported into our cells, where they enter their respective NAD+ pathways, excluding NMN (Covarrubias et al., 2020). In human cells, NMN must first be converted into NR (nicotinamide riboside) before being imported into the cell, this is performed by the 5'-nucleotidase CD73 (Covarrubias et al., 2020). This step may be different in other tissues and mammals (Covarrubias et al., 2020). The NAM salvage pathway utilizes the leftover NAD+ from enzymes to recycle for reuse in other cells and organelles (Covarrubias et al., 2020). All enzymes using NAD+ produce NAM as a byproduct, and thus is recycled into NMN and converted to NAD+ by NMN adenylyltransferases NMNAT1, NMNAT2, and NMNAT3, each of which have different locations where they perform this cycle (Covarrubias et al., 2020). These molecules also aid in the regulation of NAD+ levels in the nucleus, Golgi, and mitochondria respectively (Covarrubias et al., 2020).

NAD+ can also be created through a different cycle that uses the enzyme nicotinamide N-methyltransferase (NNMT) as a methyl donor to NAM, producing N^1-methylnicotinamide (MNAM) (Covarrubias et al., 2020). MNAM is a byproduct, and can be further oxidized, and secreted into the urine (Covarrubias et al., 2020). This conversion diverts NAM from being recycled into NAD+ and probes the idea that NMNT expression increases during obesity (Covarrubias et al., 2020). Furthermore, the NMNT expression has negative effects like reducing gene expression in metabolic and inflammatory genes, decreasing their longevity (Covarrubias et al., 2020).

Aging and the link to NAD+

Aging naturally occurs when NAD+ concentrations begin to decrease, and enzymes associated with NAD+ and its processes become altered (Covarrubias et al., 2020). Mitochondrial dysfunction and lipid accumulation are large effectors in the process of muscle aging (Chubanava & Treebak, 2023). A study found that the deterioration of mitochondrial function and muscle function in mice holds a direct link to the decrease of NAD+ (Chubanava & Treebak, 2023). This theory was tested through the imitation of aging by removing some DNA involved in the NAD synthesis pathway in mice, in turn causing these effects (Chubanava & Treebak, 2023). The results provided a link between the concentrations of NAD+ and its different forms with aging muscle function.

But what is the link between NAD+ and aging? While the cause for the decrease in NAD+ concentrations is unknown, there are a few theories as to what happens to the molecule as we age. It is known that an increase in immune activation and inflammation within the body occurs with age, and thus consumes NAD+ needed in DNA repair (NAD+ in Aging: Role of Nicotinamide Riboside and Nicotinamide Mononucleotide, n.d.). In fact, the most outstanding evidence for the decrease of NAD+ concentrations with aging is due to inflammation and the NAD+ consuming enzymes that increase with age (McReynolds et al., 2020). These enzymes, namely CD38 and PARPs, are also known to be linked to DNA damage repair and cell homeostasis (Liu & Huang, 2019). Between these functions that are onset by aging, the cells do not retain the amount of NAD+ that they once had and are forced to spread it to other processes in need.

Coupled with the fact that our general pool of NAD+ decreases with age due to these functions and sedentary activities, makes the ability to maintain an abundance of the molecule more difficult (NAD+ in Aging: Role of Nicotinamide Riboside and Nicotinamide Mononucleotide, n.d.). Because NAD+'s main functions are to aid the mitochondrial processes and the breakdown of glucose to make energy, it is pivotal that the concentration of the molecule is maintained over time (NAD+ in Aging: Role of Nicotinamide Riboside and Nicotinamide

Mononucleotide, n.d.). Additionally, NAD+ is needed for organ functions and metabolic tissue functions which keep the body at a healthy state (Covarrubias et al., 2020). NAD+ levels can be fulfilled by exercise, which keeps NAD+ levels sufficient with constant cycling of the electron transport chain (Ji & Yeo, 2022).

NAMPT, nicotinamide phosphoribosyltranserase is a rate limiting intermediate in the NAM salvage pathway, and therefore an indicator of NAD+ concentrations which was tested in some studies within the muscles of participating patients (de Guia et al., 2019). Other studies have concluded that sedentary activities can result in apoptosis, biogenesis, and deficient turnover in the mitochondria, resulting in the progression of conditions like aging and skeletal muscle atrophy (Liang et al., 2021)). NAD+ functions in the muscles by providing electrons to the electron transport chain which powers the production of ATP used in muscle contractions (McReynolds et al., 2020). These electrons are sourced from the breakdown of sugars in glycolysis and the Kreb's cycle, as well as other metabolic cycles (McReynolds et al., 2020).

Movement of muscles generates the electron transport chain and in turn, creating more electron carriers. Aerobic exercise can increase this energy production, and in turn increase oxygen consumption which drives homeostasis in cells (Liang et al., 2021)). Specific training exercises like resistance training were found to increase the NAMPT levels in older adults by 30% (de Guia et al., 2019). NAMPT levels can conclude that aging significantly reduces the NAD+ salvage pathway and the NAM recycling pathway, resulting in muscle degradation over time (Ji & Yeo, 2022). Additionally, a constant supply of NAD+ is needed in the muscles to prevent muscle degradation, resulting in these lower concentrations of the molecule (Ji & Yeo, 2022). Finally, NAD+ can be absorbed in the gut through supplementation and shows potential in being a sustainable regenerative source of NAD+ in older individuals (Fang et al., 2017). In model organisms, NAD+ supplementation has improved the health and lifespan of the organism and effected muscle strength and mitochondrial functions (Fang et al., 2017). These preventions can delay the effects of aging within the body, and in turn, improve the health and wellbeing of the subject.

Conclusion

Many studies have proved the link between NAD+ and the aging process. Through an increasing amount of NAD+ dependent enzymes, DNA repair, and metabolic processes, the concentrations of NAD+ decrease as these properties become more demanding with age (Aman et al., 2018). The effect of antioxidant deprivation and inflammation within the body promotes the use of NAD+, removing the high concentrations from regular metabolic functions that use the electron carriers (McReynolds et al., 2020). Finally, through the practice of an active lifestyle and NAD+ supplementation, it is possible to delay muscle degradation and the aging effect within the body (NAD+ in Aging: Role of Nicotinamide Riboside and Nicotinamide Mononucleotide, n.d.). In the future, studies can be conducted to explore the types of supplied NAD+ and how we can continue to benefit from the consumption of NAD+ throughout the body to maintain cell homeostasis as we age.

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