NAD - Abstracts - 5/2020

Eur J Pharmacol. 2020 Apr 28:173158. doi: 10.1016/j.ejphar.2020.173158. [Epub ahead of print]

Therapeutic potential of nicotinamide adenine dinucleotide (NAD).

Nicotinamide adenine nucleotide (NAD) is a small ubiquitous hydrophilic cofactor that participates in several aspects of cellular metabolism. As a coenzyme it has an essential role in the regulation of energetic metabolism, but it is also a cosubstrate for enzymes that regulate fundamental biological processes such as transcriptional regulation, signaling and DNA repairing among others. The fluctuation and oxidative state of NAD levels regulate the activity of these enzymes, which is translated into marked effects on cellular function. While alterations in NAD homeostasis are a common feature of different conditions and age-associated diseases, in general, increased NAD levels have been associated with beneficial health effects. Due to its therapeutic potential, the interest in this molecule has been renewed, and the regulation of NAD metabolism has become an attractive target for drug discovery. In fact, different approaches to replenish or increase NAD levels have been tested, including enhancement of biosynthesis and inhibition of NAD breakdown. Despite further research is needed, this review provides an overview and update on NAD metabolism, including the therapeutic potential of its regulation, as well as pharmacokinetics, safety, precautions and formulation challenges of NAD supplementation.

Neurochem Res. 2019 Oct;44(10):2280-2287. doi: 10.1007/s11064-019-02729-0. Epub 2019 Jan 19.

Multi-targeted Effect of Nicotinamide Mononucleotide on Brain Bioenergetic Metabolism.

Dysfunctions in NAD+ metabolism are associated with neurodegenerative diseases, acute brain injury, diabetes, and aging. Loss of NAD+ levels results in impairment of mitochondria function, which leads to failure of essential metabolic processes. Strategies to replenish depleted NAD+ pools can offer significant improvements of pathologic states. NAD+ levels are maintained by two opposing enzymatic reactions, one is the consumption of NAD+ while the other is the re-synthesis of NAD+. Inhibition of NAD+ degrading enzymes, poly-ADP-ribose polymerase 1 (PARP1) and ectoenzyme CD38, following brain ischemic insult can provide neuroprotection. Preservation of NAD+ pools by administration of NAD+ precursors, such as nicotinamide (Nam) or nicotinamide mononucleotide (NMN), also offers neuroprotection. However, NMN treatment demonstrates to be a promising candidate as a therapeutic approach due to its multi-targeted effect acting as PARP1 and CD38 inhibitor, sirtuins activator, mitochondrial fission inhibitor, and NAD+ supplement. Many neurodegenerative diseases or acute brain injury activate several cellular death pathways requiring a treatment strategy that will target these mechanisms. Since NMN demonstrated the ability to exert its effect on several cellular metabolic pathways involved in brain pathophysiology it seems to be one of the most promising candidates to be used for successful neuroprotection.

Biogerontology. 2019 Aug;20(4):381-395. doi: 10.1007/s10522-019-09805-6. Epub 2019 Mar 5.

Nicotinamide adenine dinucleotide emerges as a therapeutic target in aging and ischemic conditions.

Nicotinamide adenine dinucleotide (NAD+) has been described as central coenzyme of redox reactions and is a key regulator of stress resistance and longevity. Aging is a multifactorial and irreversible process that is characterized by a gradual diminution in physiological functions in an organism over time, leading to development of age-associated pathologies and eventually increasing the probability of death. Ischemia is the lack of nutritive blood flow that causes damage and mortality that mostly occurs in various organs during aging. During the process of aging and related ischemic conditions, NAD+ levels decline and lead to nuclear and mitochondrial dysfunctions, resulting in age-related pathologies. The majority of studies have shown that restoring of NAD+ using supplementation with intermediates such as nicotinamide mononucleotide and nicotinamide riboside can be a valuable strategy for recovery of ischemic injury and age-associated defects. This review summarizes the molecular mechanisms responsible for the reduction in NAD+ levels during ischemic disorders and aging, as well as a particular focus is given to the recent progress in the understanding of NAD+ precursor's effects on aging and ischemia.

J Biomed Sci. 2019 May 11;26(1):34. doi: 10.1186/s12929-019-0527-8.

Implications of altered NAD metabolism in metabolic disorders.

Nicotinamide adenine dinucleotide (NAD) is an important coenzyme that participates in various energy metabolism pathways, including glycolysis, β-oxidation, and oxidative phosphorylation. Besides, it is a required cofactor for post-translational modifications such as ADP-ribosylation and deacetylation by poly (ADP-ribose) polymerases (PARPs) and sirtuins, respectively. Thus, NAD regulates energy metabolism, DNA damage repair, gene expression, and stress response through these enzymes. Numerous studies have shown that NAD levels decrease with aging and under disturbed nutrient conditions, such as obesity. Additionally, a decline in NAD levels is closely related to the development of various metabolic disorders, including diabetes and fatty liver disease. In addition, many studies have revealed that administration of NAD precursors, such as nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR), efficiently increase NAD levels in various tissues and prevent such metabolic diseases. These NAD precursors are contained in natural foods, such as cow milk, vegetables, and meats. Therefore, altered NAD metabolism can be a practical target for nutritional intervention. Recently, several human clinical trials using NAD precursors have been conducted to investigate the safety, pharmacokinetics, and efficacy against metabolic disorders such as glucose intolerance. In this review, we summarize current knowledge on the implications of NAD metabolism in metabolic diseases and discuss the outcomes of recent human clinical trials.

Cell Metab. 2018 Mar 6;27(3):529-547. doi: 10.1016/j.cmet.2018.02.011.

Therapeutic Potential of NAD-Boosting Molecules: The In Vivo Evidence.

Nicotinamide adenine dinucleotide (NAD), the cell's hydrogen carrier for redox enzymes, is well known for its role in redox reactions. More recently, it has emerged as a signaling molecule. By modulating NAD+-sensing enzymes, NAD+ controls hundreds of key processes from energy metabolism to cell survival, rising and falling depending on food intake, exercise, and the time of day. NAD+ levels steadily decline with age, resulting in altered metabolism and increased disease susceptibility. Restoration of NAD+ levels in old or diseased animals can promote health and extend lifespan, prompting a search for safe and efficacious NAD-boosting molecules that hold the promise of increasing the body's resilience, not just to one disease, but to many, thereby extending healthy human lifespan.