NIACINAMIDE/NICOTINAMIDE/NAM

NAM and Mitochondrial Energetics

The gut microbiota-derived vitamin, Niacinamide/Nicotinamide/NAM serves as a precursor for NAD+, the classic coenzyme that drives REDOX reactions and OXPHOS energetics. A healthy microbiota produces more NAM, and thus more NAM-derived metabolites that produce NAD+, than does a healthy diet. But patients with Metabolic Associated Fatty Liver Disease (MAFLD), are deficient.

Studies show that supplementing with specific microbiota restores NAM and NAM-derivatives, and thus NAD+ production in the pancreas.

The gut microbiome has a unique NAD+ metabolic pathway, which yields major improvements in metabolic flexibility. Supplementing with NAM not only exerts a direct effect on the liver by its vitamin effect, but just as significantly further activates the gut microbiota to produce more NAM and NAM metabolites, and thus the synthesis of NAD+. So, an NAM supplement not only feeds the host but feeds the host secondarily by feeding the host's microbiota in a virtuous cycle.

NAD+, one major factor in cellular energetics via OXPHOS of the Electron Transport Chain (ETC), decreases with age. Why in particular does the NAD+ level drop in parallel with the aging process in the brain and the heart and other tissues? Aging is associated with an increased activity of the enzyme CD38. That enzyme consumes/degrades NAD+. And what causes an increase in CD38 enzyme? There is a combination of three factors …

- First, the declining energetics via the ETC itself causes an excess of CD38 in a vicious cycle, with CD38 further inhibiting the ETC.

- Second, the process of INFLAM-AGING via the Nutri-Spec model of Endogenous INFLAM-AGING causes a steady build-up of CD38.

- Finally, CD38 accumulates excessively as a result of insufficient autophagy --- the process by which cells detoxify, recycle, and eliminate cellular waste.

NAM gives the additional benefit of actually decreasing CD38, the cause of the NAD+ declining with age.

Oxidizing agents such as CoQ 10, Vitamin K, Methylene blue, and the tetracycline family of antibiotics are all effective at raising the NAD+/NADH ratio, but they achieve that by simply increasing the oxidation of NADH back into NAD+. In contrast, NAM actually increases the absolute quantity NAD+.

Niacinamide supplementation not only increases NAD+ directly, thus improving mitochondrial energetics, but Niacinamide has the additional benefit of inhibiting the NAD-consuming enzymes PRP-1, CD38, and Sirtuins.

Xue, Yongquan, et al. *A combination of nicotinamide and D-ribose is safe and effective to increase NAD+ metabolome in healthy middle-aged adults: A randomized triple-blind, placebo-controlled study, cross-over pilot trial.* Nutrients. 2022 May 26;14(11):2219. https://pmc.ncbi.nlm.nih.gov/articles/PMC9183138/.

Subjects supplementing with 240 mg Niacinamide, twice daily for just 1 week, increased mitochondrial energetics by boosting NAD+. Subjects were healthy men and women between the ages of 36 and 65. Compared to controls, test subjects showed significant reduction in elevated glucose, improved insulin sensitivity, and better glucose tolerance; they also increased Glutathione, and increased ATP while at the same time, there was significant reduction of the stress hormone Cortisol.

Subjects also completed the Checklist Individual Strength questionnaire, measuring physical fatigue, mental concentration, motivation, and physical activities, with significant increases in score after less than 1 week of supplementation.

The decrease in the stress hormone Cortisol is clinically significant. Cortisol is an adrenal stress hormone that stimulates catabolism, and releases Glucose into the bloodstream. Lifting the ATP and NAD+ and Glutathione with Niacinamide supplementation reduces Sympathetic Nervous System activity, resulting in less Cortisol stimulation as well. Reduction of post-prandial Glucose by Niacinamide supplementation also indicates metabolic stress release in the sense that it alleviates any perceived need for Cortisol secretion.

Chengting Luo, et al. Nicotinamide Reprograms Adipose Cellular Metabolism and Increases Mitochondrial Biogenesis to Ameliorate Obesity. J Nutr Biochem. 2022 Sep:107:109056. https://pubmed.ncbi.nlm.nih.gov/35609856/

Using a mouse model of human obesity, this study demonstrates remarkable effects of Niacinamide supplementation on decreasing obesity, increasing lean body mass (in the absence of any exercise regimen), improving Insulin Resistance and Glycemic control, and restoring liver function in test animals with compromised liver function from a high-fat diet. Mice were divided into 3 groups: a control group on normal chow and no NAM supplementation; a group on normal chow with NAM supplementation; a group made obese with a high-fat diet and then supplemented with NAM. After only 3 weeks of NAM supplementation at a human equivalent dose of less than 200mg/day:

- Fat mass in the obese group was decreased by 47% while lean mass increased 1.4-fold.

- The test group on normal chow but with NAM supplementation also showed a significant decrease in fat mass. Mass of subcutaneous adipose tissue, abdominal adipose tissue, brown adipose tissue, and liver fat mass were all decreased.

- NAM lowered the Glucose level of obese mice at each time point in a glucose tolerance test. The hair color of the obese mice returned to the black, glossy quality of the control group, with less oil on the surface that resulted from a high-fat diet.

- The decreased fat mass and improved lean mass were achieved even though the food intake between the obese group and the control group was the same.

- In the obese group, the enzyme LDH was decreased, as was Uric Acid.

- The NAM treatment did not alter the quantity of Glycolysis Energetics. Rather, it increased the NAD+ directly, and increased NAMPT, the enzyme that enhances NAD+ synthesis.

-NAM supplementation increased Carnitine synthesis in the obese mice, thus facilitating β-oxidation of Fatty Acids.

- NAM dramatically increased proteins associated with mitochondrial OXPHOS, with the Electron Transport Chain fed by both Fatty Acid β-oxidation and Krebs Cycle Glucose oxidation. NAM increased O2 consumption and CO2 production.

- Amazingly, the NAD+ in high-fat diet obese mice was increased 32-fold. NAM supplementation has a direct effect on adipose tissue. It reduces fat mass and improves glucose tolerance in obese mice. NAM supplementation upregulates mitochondrial proteins in adipose tissue and thus increases mitochondrial biogenesis.

The overall effect of NAM supplementation is to increase OXPHOS, increase Fatty Acid Oxidation, and increase Krebs Cycle energy production. Additionally, NAM also increases glucose-derived amino acids to enhance Glutathione synthesis in maintaining cellular REDOX homeostasis.

In summary, NAM reprograms adipose cellular metabolism, enhancing adipose mitochondrial functions to ameliorate symptoms associated with obesity.

This study also confirms that the NAD+ levels in adipose tissue, liver, brain, and muscle is much lower in obese subjects, and that the mechanism by which exercise and calorie restriction benefit metabolic disorders is by increasing NAD+.

NAD+ synthesis in adipose tissue muscle and brain relies on circulating NAM. Treatment of aging mice with NAM prevents hepatic steatosis, and improves liver glucose metabolism by inhibiting hepatic lipid synthesis. NAM increases lipid catabolism by upregulating genes associated with carnitine synthesis in the liver and in muscle of the obese.

In summary, NAM supplementation reverses obesity and its comorbidities by boosting NAD+, enhancing oxidation of fatty acids, and increasing GSH biosynthesis.

Soo Jin Yang, et al. Nicotinamide Improves Glucose Metabolism and Affects the Hepatic NAD-Sirtuin Pathway in a Rodent Model of Obesity and Type 2 Diabetes. J Nutr Biochem. 2014 Jan;25(1):66-72.
https://pubmed.ncbi.nlm.nih.gov/24314867/

NAM exerts its physiological function as a precursor of NAD. Sirtuins, which are NAD-dependent deacetylases, regulate glucose and lipid metabolism, and are implicated in the patho-physiology of aging, diabetes, and hepatic steatosis. In obese Type 2 Diabetic mice, NAM supplementation affects glucose control significantly. NAM:

- Improves the glucose tolerance test
- Decreases serum fasting glucose
- Decreases serum fasting insulin
- Decreases Insulin Resistance
- While yielding higher levels of serum adiponectin in the liver.

As regards the NAD-sirtuin pathway, supplementation increases NAD, increases the NAD/NADH ratio, and increases Sirtuin 1, 2, 3, and 6. These improvements are accompanied by increased mitochondrial DNA. NAM supplementation is more effective than supplementation with Nicotinic Acid.

NAM has been employed in mice to elevate NAD+ metabolism and improve health in models of Metabolic Stress. Particularly, increased NAD+ allows mice to resist weight gain, prevent noise-induced hearing loss, and maintain the regenerative potential of stem cells with age --- providing a longevity advantage. The data indicate that the level of liver NADP+ and NADPH, which are required for resistance to ROS–mediated Exogenous INFLAM-AGING, are severely challenged by diet-induced obesity, and that glycemic control is maintained by NAM supplementation.

Niacinamide supplementation is shown in human clinical trials to offer other benefits in addition to increasing NAD+. Increased acetyl-L-carnitine in skeletal muscle, plus changes in body composition and sleeping metabolic rate are reported in studies on NAM supplementation in otherwise healthy obese humans.

NAM and INFLAM-AGING

Yumin Qiu, et al. NAD+ Exhaustion by CD38 Upregulation Contributes to Blood Pressure Elevation and Vascular Damage in Hypertension. Signal Transduct Target Ther. 2023 Sep 18;8(1):353. https://pubmed.ncbi.nlm.nih.gov/37718359/

The NAD+ level is about 50% lower in those with CVD. Hypertension in endothelial cells is directly controlled by NAD insufficiency. Supplementation with an NAD+ precursor returns NAD+ to healthy levels, while at the same time lowering hypertension and inflammatory markers of vascular damage.

The deficient NAD+ is directly correlated with excess CD38 enzyme that consumes/degrades NAD+. Niacinamide supplementation not only increases NAD+ but also is an inhibitor of CD38.

It is an excess activation of macrophages that releases the proinflammatory substances, particularly IL-6 and IL-1β, that cause vascular degeneration and the inflammatory breakdown of the endothelium. That macrophage-mediated inflammatory reaction increases the expression of CD38 enzymes, which depletes NAD+ in the endothelial cells, increasing their susceptibility to inflammatory degeneration.

NAD+ varies inversely with blood pressure. NAD+ is depleted by 50% in hypertensive individuals relative to normotensive individuals. CD38 activation and the resulting NAD+ deregulation cause the blood pressure elevation and vascular damage. Restoring NAD+ significantly decreases systolic (but not diastolic) blood pressure.

For years researchers clung to the now-outdated model of ROS production as a cause of INFLAM-AGING. It was incorrectly concluded that the inflammatory mechanism of aging is produced by over-oxidation associated with a high metabolic rate. It is now clearly established that the opposite is the case --- it is sluggish metabolism, not a hypermetabolism, that causes Oxidative Stress (and Reductive Stress).

The old theory led to the conclusion that a high metabolic rate correlated with a short life span --- as if you are born with a certain charge to your battery and a certain amount of gas in your gas tank, and when you deplete one or both, life ends.

Again, the opposite is the truth. It is the insufficient oxidation of a sluggish metabolism that creates Oxidative and Reductive Stress. The higher the physiological metabolic rate, the more efficient the metabolism, and that efficiency relates to a longer life span.

All states of disease are merely focused or localized expressions of aging, so both aging and disease are manifestations of an insufficient metabolic rate. It is the metabolic rate itself that protects against diseases of toxemia, diseases of hypoxia, truly all the "Diseases of Aging" are manifestations of insufficient energetics.

In summary, the most fundamental cause of both Exogenous INFLAM-AGING (a shorter health span) and Endogenous INFLAM-AGING (a shorter life span) is a lack of energy production. And that deficient energetics is associated with a Glucogenic/Ketogenic Imbalance and/or an Anaerobic/Dysaerobic Imbalance.

The goal of maximizing health, which is to say minimizing both Exogenous and Endogenous INFLAM-AGING, is most comprehensively achieved by maintaining a high state of oxidation (that is why supplementation with antioxidants is shown to actually promote Endogenous INFLAM-AGING). The priority is to shift all redox indicators toward oxidation. That means increasing:

- the NAD/NADH ratio
- the pyruvate/lactate ratio
- the acetoacetate/β-hydroxybutyrate ratio
- the GSSG/Glutathione ratio.

Serotonin elevation is one pathophysiology indicated by the topical Niacin Test (along with elevated PGD2, PGE2, histamine, and estrogen).

Serotonin stimulates the proliferation of pulmonary smooth muscle cells, inducing fibrosis in the wall of pulmonary arteries, causing vascular remodeling and narrowing of the pulmonary arteries. The result is increased vascular resistance and pulmonary artery hypertension. The same fibrotic inflammatory consequences of excess Serotonin also apply to cardiomyocytes and the progression of Heart Failure.

The mechanism of Serotonin-induced damage is suppression of energetics by blocking NAD+. Drug researchers are working on Serotonin antagonists to protect from Heart Failure. But our health-building rather than disease-treating Metabolic

Therapy approach to excess Serotonin is to boost NAD+ via supplementation with Niacinamide and other NAD+ boosters.

Sundaram, Balamurugan, et al. *NLRC-5 Senses NAD+ Depletion, Forming a PANoptosome and Driving PANoptosis and Inflammation.* Cell. 2024 Jul 25;187(15):4061-4077.e17. https://pubmed.ncbi.nlm.nih.gov/38878777/.

This study examines the causes of an overreactive immune system that triggers pathological inflammation and cell death, as seen in autoimmune diseases. It finds that the over-activation of immune signaling molecules triggers a self-destructive inflammatory cascade resulting from mitochondrial energy depletion. Specifically, the inflammatory reaction is associated with deficient NAD+.

But the important part of this study is its finding that supplementing with the NAD+ precursor Niacinamide prevents the alarm signal from the immune system signaling molecules. To quote the conclusion of this study, "Our findings suggest Nicotinamide could be helpful in treating inflammatory diseases."

Li, Wenli et al. *NAD supplementation alleviates intestinal barrier injury induced by ethanol via protecting epithelial mitochondrial function*. Nutrients. 2022 Dec 30;15(1):174. https://pmc.ncbi.nlm.nih.gov/articles/PMC9823589/.

Leaky Gut, the absorption of endotoxins (lipopolysaccharide) from intestinal gram-negative bacteria through the intestinal epithelium, is a primary driver of INFLAM-AGING. Healing of the gut lining, decreasing the systemic inflammation associated with the Gut-Immune Axis, and restoring a healthy non-toxic microbiota is a primary focus of Nutri-Spec Metabolic Therapy.

But the question arises, what causes Leaky Gut? Is the unhealthy microbiota cause or effect of endotoxemia? The answer is it is both. But there is a more fundamental cause of Leaky Gut syndrome --- deficient mitochondrial energetics in the epithelial cells of the intestine.

That deficient mitochondrial ATP production involves the depletion of NAD+, and responds clinically to supplementation of NAD+ boosters such as Niacinamide. NAD+ booster supplementation elevates the depleted NAD+ level in intestinal epithelial cells in test animals with gut lining damaged by a high alcohol diet. The ATP level actually increased higher than that in healthy control animals.

Additional benefits to mitochondria are shown by increases in mitochondrial enzyme elevation and increased mitochondrial DNA number.

MAFLD (Metabolic-Associated Fatty Liver Disease) shows abnormal production of bile acids from cholesterol. Also, intestinal epithelial barrier damage is a key factor in MAFLD, which can result in increased risk of metabolites of bacterial origin and microbial translocation from the gut.

Toxic substances released from the microbiota, and which have a direct mitochondrial effect, include lipopolysaccharide (endotoxin), endogenous ethanol, and TMAO. These toxins are known to inhibit mitochondrial respiration, increase oxidative stress, and impair mitochondrial quality control. Mitochondrial function can be preserved to some degree by supplementation with Nicotinamide, and by the SCFAs, particularly Butyrate, produced by healthy microbiota.

Unhealthy gut bacteria produce endogenous ethanol, and the level of ethanol is high enough in those with MAFLD, that some researchers have described MAFLD as Endogenous Alcohol-Associated Fatty Liver Disease. Ethanol-producing bacteria significantly increase hepatic steatosis, inflammation, and fibrosis by an identical mechanism to alcohol ingestion.

The gut microbiota-derived vitamin, Nicotinamide (NAM) serves as a precursor for NAD+, the classic coenzyme that drives REDOX reactions and OXPHOS energetics. A healthy microbiota produces even more NAM, and thus more NAM-derived metabolites that produce NAD+, than does a healthy diet. But patients with MAFLD, are deficient.

Studies show that supplementing with specific probiotics restores NAM and NAM-derivatives, and thus NAD+ production in the pancreas.

The gut microbiome has a unique NAD+ metabolic pathway, which yields major improvement in metabolic flexibility. Supplementing with NAM not only exerts a direct effect on the liver by its vitamin effect, but just as significantly further activates the gut microbiota to produce more NAM and NAM metabolites and thus the synthesis of NAD+. So, an NAM supplement not only feeds the host but feeds the host secondarily by feeding the host's microbiota in a virtuous cycle.

Boles, Nathan C., et al. *Epigenomic and Transcriptomic Changes During Human RPE EMT in a Stem Cell Model of Epiretinal Membrane Pathogenesis and Prevention by Nicotinamide*. Stem Cell Reports. 2020 Apr 2;14(4):631–647. https://pmc.ncbi.nlm.nih.gov/articles/PMC7160390/.

This study shows that NAM supplementation has anti-fibrotic effects, both by improving mitochondrial energetics as an NAD+ booster, but also via inhibition of the TGF-β pathway of inflammation. To illustrate, these anti-fibrotic effects protect the eye from fibrotic eye disease such as glaucoma, but it has also shown benefits in other fibrotic diseases such as autoimmune scleroderma, with benefits to wound healing and minimization of scar tissue.

Buhse, Frederike. *Faster Recovery From COVID-19 Through Targeted Use of High-Dose Vitamin B3 in the Gut.* Precision Medicine in Chronic Inflammation. Dec 2025. https://idw-online.de/de/news851759.

This study shows that 500 mg of Niacinamide taken twice daily for 4 weeks results in quicker recovery from COVID-19, and that the effects are still evident at 6 months follow-up. This sample population particularly includes smokers and those with other chronic respiratory pathologies who are at high risk, not only for severe consequences of COVID, but also at risk for Long COVID. The subjects regained normal physical performance after only 2 weeks of the 4-week study. Even subjects with the highest risk of Long COVID, responded to the 4-week trial with far fewer post-COVID symptoms.

The faster and more permanent recovery from COVID is attributed to one or both of two factors. First, NAM is the precursor to NAD+, and is thus a major booster to mitochondrial energetics.

The second mechanism by which NAM is beneficial is due to its influence on microbiota. The microbiota of COVID patients typically shows an emergency metabolism, lasting for weeks, in which the Microbiota-Immune Axis attempts to compensate for deficits in certain metabolic factors by upregulating other metabolic processes. None of these emergency microbiota-driven adaptations were evident in the NAM study group --- presumably because metabolic deficiencies can be compensated by administering the NAM. The head researcher stated, “This is the first time we have shown that influencing the microbiome, in this case through supplementation of a nutrient, can have a positive effect on viral infection. This is an important milestone in clinical research.”

Jeimy Katherine Torres-Mendez, et al. Nicotinamide Prevents Diabetic Brain Inflammation via NAD+-Dependent Deacetylation Mechanism. Nutrients. 2023 Jul 9;15(14):3083. https://pubmed.ncbi.nlm.nih.gov/37513501/

This study investigates the effect of NAM supplementation on the development of brain inflammation and microglial activation in a mouse model of Type 1 Diabetes. NAM supplementation significantly increases the NAD+ content in the brain more than 3-fold. Supplementation also decreases markers of inflammation (as measured by TNF-alpha) by up to 46%. It also increases microglial activation by as much as 50%. These benefits are accompanied by a significant decreased signaling of the inflammatory marker NFkB, and that decrease in NFkB inversely correlates with the increase of NAD+, suggesting increased activity of NAD+-dependent deacetylases in the brain. The decrease in brain inflammation associated with an increase in NAD+ suggests an increased action of sirtuin signaling.

Tetsushi Kataura, et al. Autophagy Promotes Cell Survival by Maintaining NAD Levels. Dev Cell. 2022 Nov 21;57(22):2584-2598.e11. https://pubmed.ncbi.nlm.nih.gov/36413951/

This study emphasizes the essentiality of autophagy in all cells as the catabolic process that promotes the clearance of surplus or damaged intracellular components. Loss of autophagy in age-related pathologies contributes to tissue degeneration, and the mechanism is largely by failure to maintain adequate NADH in mitochondrial OXPHOS. NAD is critical for cell survival. In autophagy deficiency, loss of mitochondrial quality control triggers hyperactivation of stress responses mediated by the enzymes that break down NAD (--- the PARP and the SIRT families). Autophagy deficiency resulting in depletion of the NAD (H) pool by these enzymes ultimately causes mitochondrial membrane depolarization and cell death.

Supplementation with NAC (as found in Rejuvenator & Activator) protects NAD (H) from damaging enzymes. Even more effective than NAC in rescuing NAD (H) levels, and preventing cell death is supplementing with NAM.

NAM and Brain Health

Liu, Zhuxi, et al. *Nicotinamide, a vitamin B3, ameliorates depressive behaviors independent of SIRT1 activity in mice*. Mol Brain. 2020 Nov 23;13:162. https://pmc.ncbi.nlm.nih.gov/articles/PMC7686777/.

In a mouse model that correlates directly with long-term depression in humans, it is found that depression is essentially caused by a low-energy state in the brain. One of the most significant differences in the brains of depressed vs. normal mice is an extremely low level of Niacinamide, accompanied by a low level of NAD+ which is derived from Niacinamide, along with significantly lower levels of ATP energy production. Supplementation of depressed mice with Niacinamide at a human equivalent dose of about 1000 mg daily reversed all depressive behaviors, while it increased brain tissue levels of NAM, NAD+, and ATP. This study cites previous studies showing that NAM can improve the incidence of depression in humans, and this study identifies the mechanism.

Sun, Congxin, et al. NAD Depletion Mediates Cytotoxicity in Human Neurons with Autophagy Deficiency. Cell Rep. 2023 Apr 21;42(5):112372. https://pmc.ncbi.nlm.nih.gov/articles/PMC10556436/.

Brain cells die from malfunction of autophagy, the process by which cells break down cellular waste and generate energy for continued survival. Metabolic failure arising from loss of autophagy is particularly detrimental to brain cells. When autophagy is deficient, levels of NAD+ fall, causing deficient mitochondrial energetics. It is the deficiency of NAD that is identified as the mediator of cell death.

When autophagy is deficient, NAD required for energetics is consumed by hyperactivity of enzymes such as Sirtuins and PARPs. Boosting NAD improves the survival of neurons suffering from autophagy deficiency.

This study reinforces the long-understood association between deficient autophagy and neurodegenerative diseases by magnifying the mechanism of neurodegeneration. It finds that depletion of NAD due to hyperactivation of NAD-consuming enzymes triggers cell death via mitochondrial depolarization. Boosting intracellular NAD improves cell viability by restoring mitochondrial energetics in neurons.

Healthy autophagy promotes metabolic homeostasis by recycling cytoplasmic macromolecules, and autophagy deficiency causes metabolic stress. Specifically, there is a nucleic acid recycling defect in autophagy-deficient cells. There is also deficiency of several intermediates of both glycolysis and the Krebs Cycle. There is a depletion of ATP and NADH in autophagy-deficient neurons despite compensatory increase in glucose metabolism. In particular, there is an excess dominance of glycolysis over Krebs Cycle energetics (an Anerobic Metabolic Imbalance). In other words, this study shows a greater use of glucose via glycolysis in autophagy-deficient neurons as they attempt to cope with their metabolic stress.

However, despite this compensation, the reduction in almost all Krebs Cycle metabolites shows that this response is insufficient compensation for the loss of autophagy-derived metabolites. Despite increased glucose contribution to the glycolytic and Krebs Cycle metabolic pathways, there is significant depletion of ATP, ADP, NAD+, and NADH, showing that --- specifically with the lower ATP and NADH --- there is an energetic deficit. The NADH depletion in particular that results from loss of autophagy is associated with increased cytotoxicity (the accumulation of toxic metabolic end-products resulting from inefficient mitochondrial energy production).

Looking at amino acid metabolism, this study finds that glycine (found in Rejuvenator and Activator, and as Magnesium glycinate in Complex S, Complex P, and Activator) in particular is most significantly depleted by deficient autophagy. But, the neurons show an increased uptake of the excitotoxic amino acids aspartate and glutamate, and are thus toxin-impaired.

Both NADH (the reduced form of NAD) and NAD+ (the oxidized form of NAD) are deficient, indicating exhaustion of the total pool of NAD (H). Boosting NADH by supplementing with NAM improves cell viability. NAM supplementation increases the NADH level via the salvage pathway.

The depletion of the NAD and NADH pool in deficient autophagy depends on the autophagy-deficient state causing increased levels of NAD-consuming enzymes (--- such as CD3, SIRT1, SIRT2, PARP1, and PARP2). Persistent DNA damage is the result.

While NAD+ is significantly decreased in the cytosol, NADH is predominantly depleted in the mitochondria of autophagy-deficient neurons. It is oxidation of NADH that mediates the generation of mitochondrial membrane potential, which

activates the flow of electrons (donated by NADH) through the ETC (Electron Transport Chain) (coupled to proton pumping across the inner mitochondrial membrane). It is that mitochondrial membrane electrochemical protein gradient that ultimately drives ATP production in the mitochondria.

Furthermore, loss of autophagy leads to inefficient mitophagy, resulting in the accumulation of damaged mitochondria. Boosting NAD (H) with NAM restores mitochondrial respiration to normal. This process is especially important for neuron cells, which have high energy demand relative to other cell types, and are greatly reliant on mitochondrial OXPHOS for energy production.

Boosting NAD+ and NADH with boosters such as NAM restores the autophagy function of clearing aggregated proteins. The toxic accumulations associated with aging and neurodegenerative disease, including beta-amyloid accumulation are attenuated.

In summary: Both "normal" aging and neurodegenerative diseases are associated with impaired autophagy activity, accumulation of misfolded protein aggregates, lower NAD+ and NADH levels, and mitochondrial dysfunction --- resulting in cytotoxicity, production of Reactive Oxygen Species, and mitochondrial dysfunction. These results of autophagy deficiency can be largely mitigated by boosting the NAD (H) pool with NAM supplementation, and perhaps with glycine supplementation, and most definitely with specific probiotic + prebiotic supplements.

Quoting the study, "NAD can be boosted through the use of targeted therapeutics such as supplementation with NAD precursors like Nicotinamide. Our research identifies the potential for drugs to slow down the NAD-eating enzymes in the PARP and Sirtuin families, which supports healthy aging and reduces risk of neurodegeneration."

Grill JD, Tam S, Thai B, et al. *A phase 2a proof-of-concept double-blind, randomized, placebo-controlled trial of nicotinamide in early Alzheimer's disease*. Presented at: AAIC 2023; June 16-20; Amsterdam, Netherlands. Abstract 77979.

This clinical trial supplemented individuals with a Clinical Dementia Rating, qualifying them as having early AD. For 12 months, they were supplemented with 1500 mg twice daily of Nicotinamide. There were no adverse events and side effects were mild. Subjects on the Niacinamide supplementation showed no

significant advance in Clinical Dementia Rating, while those on placebo showed advancing CDR scores. Previous research shows that it is the decline in NAD+ in the brain during aging that constitutes the metabolic and cellular dysfunction underlying AD and other age-associated neurological disorders. Nicotinamide is an effective NAD+ enhancer.

Chaubey, Kalyani, et al. *Pharmacologic Reversal of Advanced Alzheimer's Disease in Mice and Identification of Potential Therapeutic Nodes in Human Brain*. Cell Rep Med. 2025 Dec 22;7(1):102535. https://pmc.ncbi.nlm.nih.gov/articles/PMC12866132/.

This study shows in a mouse model of human Alzheimer's Disease that early Alzheimer's is completely reversible. The study shows clearly that Alzheimer's is a Metabolic Disease, with insufficiency of mitochondrial ATP production as the root cause of the buildup of misfolded proteins and other sources of brain cell damage. The advance of Alzheimer's is not only stopped but the condition reversed, with test animals totally regaining cognitive function when supplemented with an NAD+ booster.

SIDE NOTE 1: A few years ago two companies patented variants of Niacinamide purported to even more effectively increase NAD+. Those were Nicotinamide Riboside (NR), and Nicotinamide Mononucleotide (NMN). Each company aggressively marketed its product, and financed research to prove efficacy in increasing NAD+. Almost all the studies were on animals, and showed some beneficial increases in NAD+. There were very few studies done on human beings, and those were equivocal at best. But, there were two important qualifiers to consider here …

The doses of these products used on mice were the human equivalent doses of 2,000 – 3,000 mg. Yet most of the NR and NMN supplements on the market contain only between 100 – 250 mg. Another consideration is that the FDA has declared NMN and perhaps NR as "novel drugs", which means they can no longer be produced as nutrition supplements (--- though there are still remnant products available on the market and they are still heavily promoted).

But the big news on NR and NMN is that they do absolutely nothing that NAM doesn't do in terms of increasing NAD+. On a dose-equivalent basis, NAM yields a virtually identical increase in NAD+. Only one human study shows superior NMN metabolic and anti-aging benefits over NAM, and the NMN was administered IV, not orally. There is an even more important factor here proving the superiority of NAM over either NMN or NR …

NAD+, one major factor in cellular energetics via OXPHOS of the Electron Transport Chain (ETC), decreases with age. Why in particular does the NAD+ level drop in parallel with the aging process in the brain and the heart and other tissues? Aging is associated with an increased activity of the enzyme CD38. That enzyme consumes/degrades NAD+. And what causes an increase in CD38 enzyme? There is a combination of three factors …

- First, the declining energetics via the ETC itself causes an excess of CD38 in a vicious cycle, with CD38 further inhibiting the ETC.

- Second, the process of INFLAM-AGING via the Nutri-Spec model of Endogenous INFLAM-AGING causes a steady build-up of CD38.

- Finally, CD38 accumulates excessively as a result of insufficient autophagy --- the process by which cells detoxify, recycle, and eliminate cellular waste.

Now we get to the superiority of NAM. While NR and NMN will increase NAD+, NAM will do so as well --- but --- NAM gives the additional benefit of actually decreasing CD38, the cause of the NAD+ declining with age.

SIDE NOTE 2: Why does Niacin, as Nicotinic Acid, cause a flushing reaction, while Niacinamide/Nicotinamide (NAM) does not? The Niacin flush is caused by a carboxyl group in the pyridine nucleus of the molecule. The flush is caused by Niacin increasing both Prostaglandin D2 and serotonin --- both of which are pro-inflammatory. (PGD2 is also responsible for much of the non-sneezy sinus congestion caused by mold exposure.)

Niacin is actually an anti-metabolite at intake levels not much higher than are found a healthy diet, while NAM is a powerful metabolic activator. The problems with Niacin supplementation include …

- Increases fatigue
- Increases liver enzyme SGOT
- Increases the liver/biliary enzyme Alkaline Phosphatase
- Increases fasting glucose
- Increases immune-reactive insulin resistance
- Increases homocysteine --- an independent risk factor for CVD, and an indication of Endogenous INFLAM-AGING