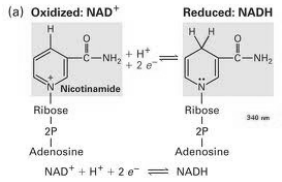
INTERNATIONAL
IV NUTRITIONAL THERAPY
GLOBAL PHYSICIAN EDUCATION

Strategies to optimize NAD/ NADH

Advanced NAD IV

/IIVNTP



Importance of NAD+/NADH

- NAD+ activates SIRT1
- NADH activates Pyruvate Dehydrogenase Complex
- High NAD/NADH ratio favors oxidation of substrates
- Low NAD/NADH results in low pyruvate and low oxaloacetate. Inhibiting glucose synthesis
- Both are substrates and allosteric effectors for many enzymes

NAD+/NADH

Optimal physiological conditions is cytosolic ratio:

700:1 (NAD+/NADH)

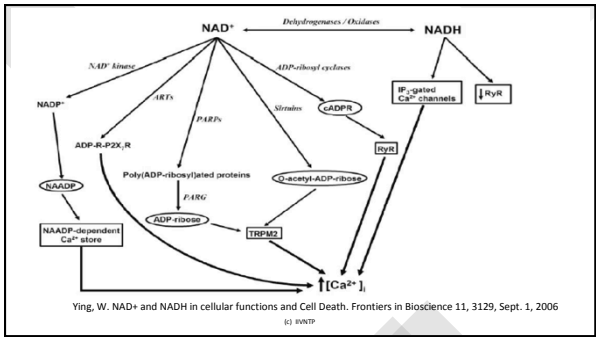
NAD+/NADH

- Nuclear membranes can be freely permeable to NAD+ and NADH.
- Mitochondria membranes are impermeable to NAD+ and NADH
- NADH can be shuttled into the mitochondria via malate-aspartate shuttle
  - This is found in neurons
  - Not found readily in astrocytes
- NAD and NADH mediate calcium homeostasis
- NAD+ can generate ADP-Ribose

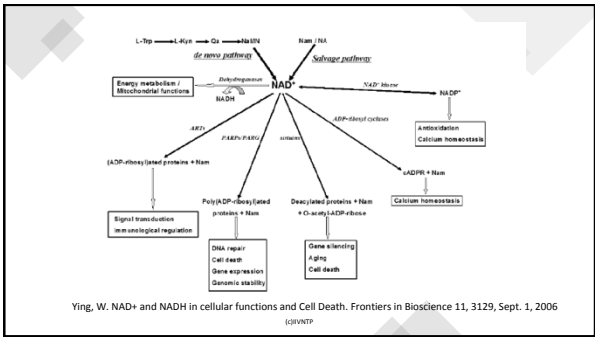
NAD/NADH

NAD+ is an oxidizing agent (accepts electrons)

NADH+ is a reducing again (donates electrons)



Ying, W. NAD+ and NADH in cellular functions and Cell Death. Frontiers in Bioscience 11, 3129, Sept. 1, 2006



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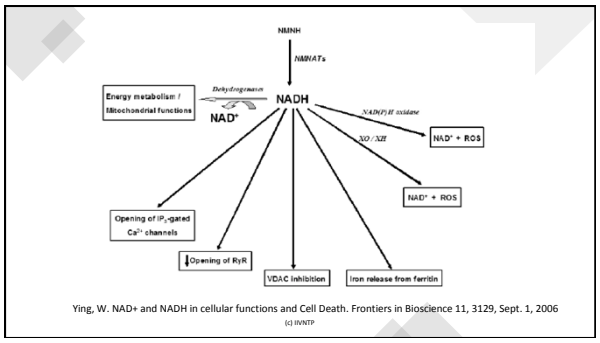
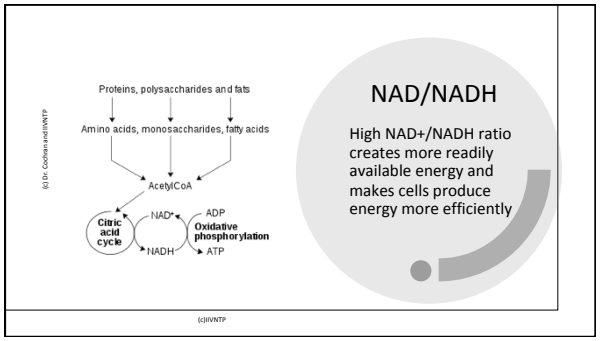


Ying, W. NAD+ and NADH in cellular functions and Cell Death. Frontiers in Bioscience 11, 3129, Sept. 1, 2006

So why do we want to optimize NAD+/NADH?



NAD/NADH

High NAD+/NADH ratio creates more readily available energy and makes cells produce energy more efficiently

So how can you increase NAD+/NADH?

Diet Strategies

- Low glucose intake (Increased AMPK and SIRT1)
- Increased Ketone bodies (Fatty acid oxidation)
- Fasting

- Caton, P et. al. Fructose induces gluconeogenesis and lipogenesis through a SIRT1-dependent mechanism. Journal of Endocrinology. DOI https://doi.org/10.1530/JOE-10-0190
- PMID: 18477450
- PMID: 18550784
- Yang, Hongying et al. Nutrient-Sensitive Mitochondrial NAD+ Levels Dictate Cell Survival. Cell. DOI https://doi.org/10.1016/j.cell.2007.07.035

Highest Foods Boosting NAD+

- Raw dairy (nicotinamide riboside)
- Fatty fish (NAD+)
- Nutritional Yeast/Fermented Foods (Niacinamide)
- Tryptophan rich foods (cherries, pumpkin, poultry, etc.)

Exercise

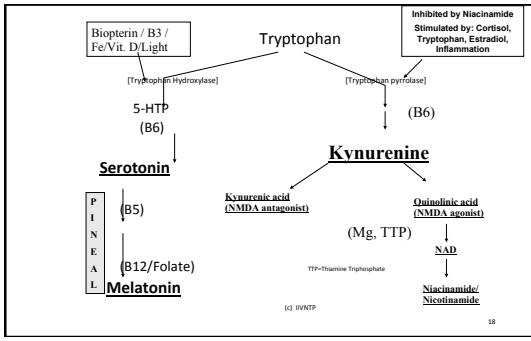
- Resting human muscle is estimated to have NAD+ concentrations of ~1.5–1.9 mmol/kg and NADH ~0.08–0.20 mmol/kg.
- This increases with greater number of slow-twitch muscle fibers

- PMID: 20197054
- PMID: 19887595
- PMID: 212709
- PMID: 1182948

Sauna (Heat or Heat Shock Therapy)

Tryptophan (De Novo Synthesis)

Requires key nutrients:
Thiamin (B1)
Riboflavin (B2)
Niacinamide (B3)
Pyridoxine (B6)
Magnesium
Carnitine



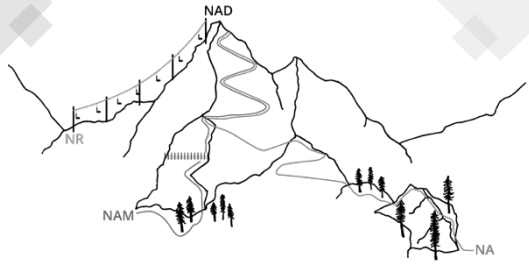
Niacinamide/Niacin (minimum 20 mg per day)

Nicotinic Acid (NA)

Niacinamide (NAM)

Nicotinamide riboside (NR)

Nicotinamide Mononucleotide (NMN)



https://www.aboutnad.com/nad-precursors

Resveratrol

- Resveratrol increases NAD+ via upregulation of NAD+ nicotinamide mononucleotide adenylyltransferase.
- Potent SIRT1 activator

Resveratrol

- Appears tolerated in IV doses up to 50 mg/kg
- Potential concern in patients with slow Phase-2 detox (high sulfation and glucuronidation detox)
- Much more that we do not know than we know!

Resveratrol

Plant-derived polyphenolic compounds, such as the stilbene resveratrol (trans-3, 4', 5-trihydroxystilbene), have been identified as potent anti-cancer agents. Extensive in vitro studies revealed multiple intracellular targets of resveratrol, which affect cell growth, inflammation, apoptosis, angiogenesis, and invasion and metastasis. These include tumor suppressors p53 and Rb; cell cycle regulators, cyclins, CDKs, p21WAF1, p27KIP and INK and the checkpoint kinases ATM/ ATR; transcription factors NF-κB, AP-1, c-Jun, and c-Fos; angiogenic and metastatic factors, VEGF and matrix metalloprotease 2/9; cyclooxygenases for inflammation; and apoptotic and survival regulators, Bax, Bak, PUMA, Noxa, TRAIL, APAF, survivin, Akt, Bcl-2 and Bcl-XL.

Athar M. et. al. Multiple molecular Targets of Resveratrol: Anti-carcinogenic Mechanisms. Arch Biochem Biophys. 2009 June 15; 486(2): 95–102. doi:10.1016/j.abb.2009.01.018.

INTRAVENOUS RESVERATROL:

- Resveratrol has great potential in the treatment of patients who have chronic illness. Intravenous data in human subjects shows it to be tolerated and safe.
- Data available suggest multiple mechanisms of action in immune-regulatory systems as well as redox balance effects.
- Three years of clinical use has revealed no adverse events when used under standard dose and administration guidelines.

INTRAVENOUS USE GUIDELINES:

Dose:

- Test dose at 1 mg/kg IV on the first day
- Subsequent doses could increase to 25 mg/kg if tolerated two times weekly

Administration:

- Intravenous dosing via either a central or peripheral line.
- Carrier solutions:
  - Per compounding pharmacy instructions
- Rate of administration: 60 to 180 minutes as tolerated by the patient
  - Monitor for signs of nausea which can be the first sign of a non-tolerated dose [3]
  - For allergic / anaphylactic reaction treat per standard protocol.
- Other IV compatibility:
  - Generally incompatible with other IV solutions in the same IV container

Screening:

- Intolerance to oral Resveratrol is a caution and may exclude use in the IV setting
- Lab studies:
  - CBC, Chemistry panel (Metabolic panel including electrolytes, bilirubin, AST/ALT/GGT, eGFR/BUN/CRE).

References:

1. Anderson P, Cochran B. Personal experiences with the clinical use of intravenous substances. AMSA, BIORC and Private clinic data. Seattle Washington, 2014

4. Walle T. et.al. HIGH ABSORPTION BUT VERY LOW BIOAVAILABILITY OF ORAL RESVERATROL IN HUMANS. DMD December 2004 vol. 32 no. 12 1377-1382. doi: 10.1124/dmd.104.000885

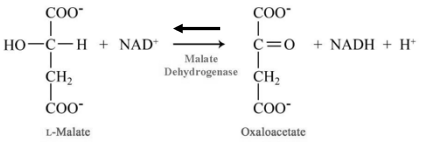
5. A. Amri et al. Administration of resveratrol: What formulation solutions to bioavailability limitations? Journal of Controlled Release 158 (2012) 182–193

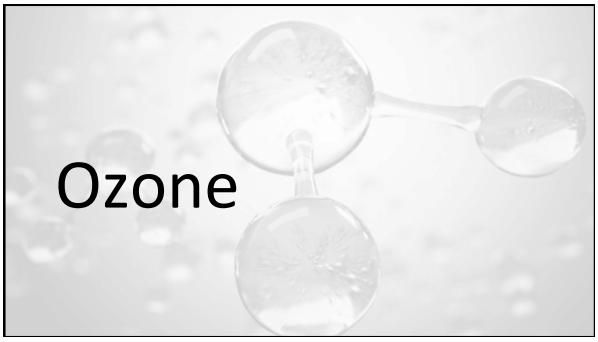
6. Baur J and Sinclair DA. Therapeutic potential of resveratrol: the in vivo evidence. NATURE REVIEWS. DRUG DISCOVERY.VOLUME 5.JUNE 2006.[493-506]

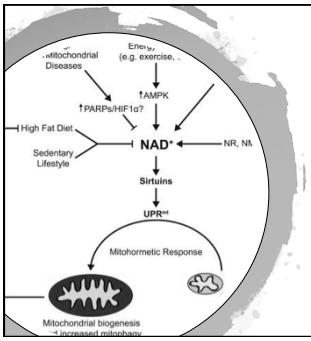
7. Das S, Lin HS, Ho PC, Ng KY. The impact of aqueous solubility and dose on the pharmacokinetic profiles of resveratrol. Pharm Res. 2008 Nov;25(11):2593-600. doi: 10.1007/s11095-008-9677-1. Epub 2008 Jul 16. PMID: 18629618

Oxaloacetate

Increases NAD+ and FOXO proteins

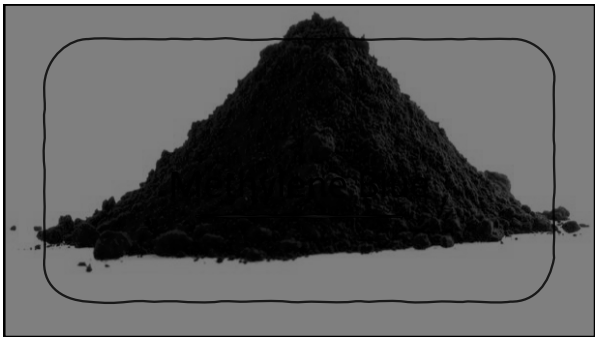


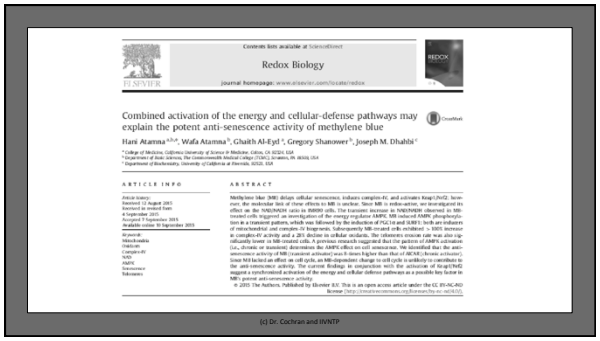




Ozone improves NAD/NADH Ratio

Ozonide + NADH = H20 + NAD + O2



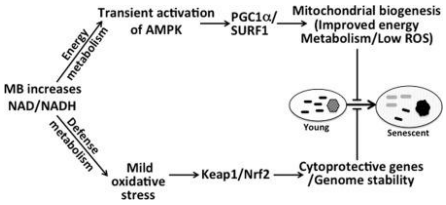


Redox Biology

Combined activation of the energy and cellular-defense pathways may explain the potent anti-senescence activity of methylene blue

(c) Dr. Cochran and IIVNTP

Methylene Blue



Methylene Blue

Mostly used for treating congenital or poison-induced methemoglobinemia.

Things that can induce methemoglobinemia

Acetaminophen	Atovaquone	Benzocaine	Buprenorphine-naloxone	Celecoxib Chloroquine Cotrimoxazole Cyclophosphamide	Dapsone
Disulfiram	EMLA cream	Flutamide	Hydrogen Peroxide	Ibuprofen	Ifosfamide
Lidocaine	Metoclopramide	Nitrates and nitrates	Nitric Oxide	Phenazopyridine	Prilocaine
Primaquine	Rasburicase	Riluzole	Sulfonamides	Tetracaine	Vitamin K1
Zopiclone					

http://www.dpic.org/article/professional/methemoglobinemia-and-medications-z

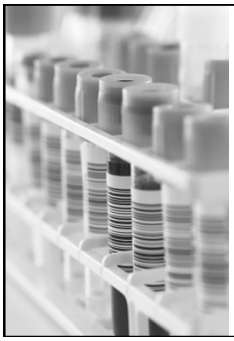
Methemoglobin (Fe3+) + NAD(P)H ------> Deoxyhemoglobin(Fe2+) + NAD

↑

MB (Methylene Blue)

Methylene Blue

- Induces complex IV
- Increases NAD/NADH
- Increase pAMPK/ AMPK
- SIRT1 activator



Labs Needed

- CBC
- CMP
- G6PD (Quantitative)

Cautions/Contraindications

- Methylene blue is MAOI
  - Cautions for Serotonin Syndrome
  - Administer 72 hours away from MAOI, SSRI, SNRI
- G6PD Deficiency
- Pregnancy

Most Common Side Effects

- Change in taste
- changes in skin color
- feeling hot or cold
- increased sweating
- loss of taste
- muscle or joint pain
- pain at the infusion site
- pain in the arms or legs

Interactions

- Acetaminophen
- Codeine
- Butalbital
- Dextromethorphan
- Phenylephrine
- Caffeine
- Doxylamine
- Guaifenesin
- Amitriptyline
- Chlordiazepoxide
- Many More…..

Methylene Blue

Oral (Dosing up to 1-2 mg/kg are tolerated well)

- Liquid (Make sure it is USP and formaldehyde free)
- Troches

Intravenous

- Supplied as 10 mg/ml
- Test dose at 10 mg or lower in 250 ml D5W
- Typical dosage is 0.5-1 mg/kg
- Max Dosage 2 mg/kg
- Administer alone in D5W
  - Normal Saline reduces solubility
  - Sterile water osmolarity too low

https://www.pdr.net/drug-summary/Methylene-Blue-1--methylene-blue-24011

Melatonin

Journal of Pineal Research / Volume 39, Issue 2 / p. 185-194

Interactions between melatonin and nicotinamide nucleotide: NADH preservation in cells and in cell-free systems by melatonin

Dun-Xian Tan, Lucien C. Manchester, Rosa M. Sainz, Juan C. Mayo, Josefa Leon, Ruediger Hardeland, Burkhard Poeggeler, Russel J. Reiter

First published: 23 May 2005
https://doi.org/10.1111/j.1600-079X.2005.00234.x
Citations: 37

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Abstract

Abstract: Interactions of melatonin and nicotinamide adenine dinucleotide (NADH) have been studied in different experimental models including NADH-promoted oxyhemoglobin oxidation, vanadate-induced NADH oxidation and paraquat-induced NADH depletion in cultured PC12 cells. Our findings indicate that melatonin preserves NADH levels under oxidative stress both in cell-free systems and in cultured PC12 cells. These interactions likely involve electron donation by melatonin and reduction of the NAD radical. As a result, the NAD radical is recycled to NADH and melatonin is oxidized to N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK). NADH is a central molecule at the crossroads between energy metabolism and the antioxidant defense system in organisms. Recycling of NADH by melatonin might improve the efficiency of NADH as an energy carrier and as an antioxidant. Interactions between melatonin and NADH may be implicated in mitochondrial metabolism.

Melatonin

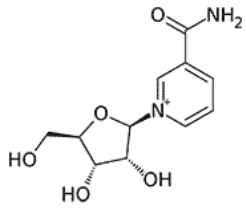
- Oral: 5-10 mg
- Rectal: 200 – 400 mg
- Topical: ? Unknown
- Intravenous:

10 mg titrated up to 50 mg in 250 ml Normal Saline (Infusion time 60-90 minutes)

Melatonin Intravenous Side Effects

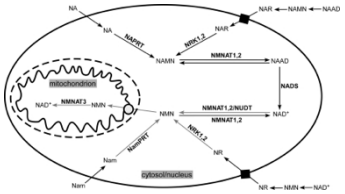
- Increased peripheral blood circulation
- Vasoconstriction in cerebral arteries and decreased body temp.
- Immune stimulatory
- Fatigue
- Drowsiness

Nicotinamide Riboside



nicotinamide riboside

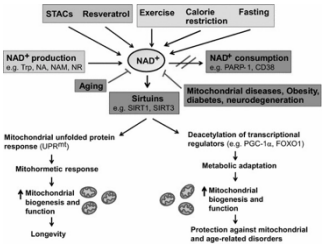
NAD+



•NAD+ is broken down extracellular to NR and this can then go into the cell, but ultimately needs to break down to NMN to enter the mitochondria

- PMID: 21504897

Summary



https://www.researchgate.net/figure/Boosting-NAD-levels-is-beneficial-for-health-and-lifespan-NAD-is-a-rate-limiting_fig1_305693771