



- Ag - Silver
- $\alpha$ -KGDH - Alpha-Ketoglutarate Dehydrogenase
- ALDH - Aldehyde Dehydrogenase
- ADP - Adenosine Diphosphate
- ATP - Adenosine Triphosphate
- Au - Gold
- cAMP-PKA - Cyclic Adenosine Monophosphate - Protein Kinase A
- Cd - Cadmium
- CD38 - Cluster of Differentiation 38 (NAD<sup>+</sup> glycohydrolase)
- CHAC1 - Glutathione-Specific gamma-Glutamylcyclotransferase 1
- CDR - Cell Danger Response
- COMPLEX I - NADH:Ubiquinone Oxidoreductase
- Cys-Gly - Cysteinyl-glycine
- DHAP - Dihydroxyacetone Phosphate
- DOPAL - 3,4-Dihydroxyphenylacetaldehyde
- eATP - Extracellular Adenosine Triphosphate
- FAD - Flavin Adenine Dinucleotide
- G3P - Glycerol 3-Phosphate
- GCL - Glutamate-Cysteine Ligase
- GGCT - gamma-Glutamyl Cyclotransferases
- GLS - Glutathione Synthase
- GPD - Glycerol-3-Phosphate Dehydrogenase
- GPx - Glutathione Peroxidase
- GR - Glutathione Reductase
- GDH - Glutamate Dehydrogenase
- GHB - gamma-Hydroxybutyrate
- GSH - Glutathione, Reduced
- GSSG - Glutathione, Oxidised (Disulfide)
- H<sub>2</sub>O - Water
- H<sub>2</sub>O<sub>2</sub> - Hydrogen Peroxide
- Hg - Mercury
- IDH - Isocitrate Dehydrogenase
- IDO1 - Indoleamine 2,3-Dioxygenase 1
- IFN - Interferon
- LDH - Lactate Dehydrogenase
- LPA - Lipoamide
- MB<sup>+</sup> - Methylene Blue
- MBH<sub>2</sub> - Leucomethylene Blue
- MDH - Malate Dehydrogenase
- Mo<sup>2+</sup> - Molybdenum Ion
- Mg<sup>2+</sup> - Magnesium Ion
- NAD<sup>+</sup> - Nicotinamide Adenine Dinucleotide (oxidised)
- NADH - Nicotinamide Adenine Dinucleotide (reduced)
- NADP - Nicotinamide Adenine Dinucleotide Phosphate (oxidised)
- NADPH - Nicotinamide Adenine Dinucleotide Phosphate (reduced)
- NADPT - NAD(P) Transhydrogenase
- NMNAT - Nicotinamide Mononucleotide Adenylyltransferase
- NOS - Nitric Oxide Synthase
- NOX - NADPH Oxidase
- OxPPP - Oxidative Pentose Phosphate Pathway
- P5P - Pyridoxal 5-Phosphate
- Pb - Lead
- PDH - Pyruvate Dehydrogenase
- pGlu - Pyroglutamate
- Pi - Inorganic Phosphate
- PRPP - 5-Phosphoribosyl-1-Pyrophosphate
- Q - Ubiquinone
- QH<sub>2</sub> - Ubiquinol
- ROS - Reactive Oxygen Species
- RNS - Reactive Nitrogen Species
- Se - Selenium
- TCA - Tricentric Acid
- THP - Tetrahydropapaveroline
- TPP - Thiamine Pyrophosphate
- UDP - Uridine Diphosphate
- UTP - Uridine Triphosphate
- Zn<sup>2+</sup> - Zinc Ion

**Description**

Acetaldehyde, glycolysis, TCA cycle flux and other mitochondrial matrix NADH generators (not shown - see Figure 17) decrease the mitochondrial NAD<sup>+</sup> pool and increase NADH pool sizes.

Complex I (NADH Dehydrogenase) normally balances NAD<sup>+</sup>:NADH redox, however is inhibited by reactive oxygen and nitrogen species, generated by mitochondrial activity and additionally by uncoupled NOS and NOX activity - promoted by interferon signalling cascades and acetaldehyde directly.

As Mitochondrial Complex I is progressively inhibited, proportional NADH pool elevation inhibits TCA cycle substrate pathways, whilst GDH + NADPT activity is increased, increasing glutamate and NADPH, thereby promoting regulatory glutathione synthesis and peroxidase, reductase activity - *unless* inhibited by low glycine and/or cysteine. Also from low Mg-ATP, Se, FAD, total NADP:NADPH pool size and/or excess heavy metals, where elevated pyroglutamate (pGlu) may also be observed.

Methylene blue concentrates in the mitochondrial matrix, providing a narrow therapeutic window for creating a parallel electron pathway to Cytochrome c and NAD<sup>+</sup> redox support.

**Connector Key:**

Path ———→

Promoted - - - - ->

Inhibited - - - - -+†

**Figure 14. Pathway Diagram:** A simplified overview of mitochondrial NAD<sup>+</sup>: NADH deficiency.  
**ME/CFS: Correcting Chronic Mitochondrial Dysfunction**  
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