



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

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

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

Where Complex I is inhibited, GDH and NADPT activity is increased by the NADH pool elevation, further increasing glutamate and the NADPH pool, promoting regulatory glutathione peroxidase and other synthesis activities.

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

Ag - Silver
α-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⁺ glycohydrolase)
COMPLEX I - NADH:Ubiquinone Oxidoreductase
DOPAL - 3,4-Dihydroxyphenylacetaldehyde
eATP - Extracellular Adenosine Triphosphate
FAD - Flavin Adenine Dinucleotide
GCL - Glutamate-Cysteine Ligase
GLS - Glutathione Synthase
GPx - Glutathione Peroxidase
GR - Glutathione Reductase
GDH - Glutamate Dehydrogenase
GHB - gamma-Hydroxybutyrate
H₂O - Water
H₂O₂ - Hydrogen Peroxide
Hg - Mercury
IDH - Isocitrate Dehydrogenase
IFN - Interferon
LPA - Lipoamide
MB⁺ - Methylene Blue
MBH₂ - Leucomethylene Blue
MDH - Malate Dehydrogenase
Mo²⁺ - Molybdenum Ion
Mg²⁺ - Magnesium Ion
NAD⁺ - 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
Pb - Lead
P5P - Pyridoxal 5-Phosphate
PDH - Pyruvate Dehydrogenase
Pi - Inorganic Phosphate
PRPP - 5-Phosphoribosyl-1-Pyrophosphate
Q - Ubiquinone
QH₂ - Ubiquinol
ROS - Reactive Oxygen Species
RNS - Reactive Nitrogen Species
Se - Selenium
TCA - Tricaric Acid
THP - Tetrahydropapaveroline
TPP - Thiamine Pyrophosphate
Zn²⁺ - Zinc Ion