

Connector Key:

Path Promoted ----> Inhibited ------

Figure 14. Pathway Diagram: A simplified overview of mitochondrial NAD+:NADH deficiency.

ME/CFS: Correcting Chronic Mitochondrial Dysfunction

Author: Joshua Leisk ©2025, https://bornfree.life [DRAFT / INCOMPLETE - may contain errors]

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, driving downstream 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.

α-KGDH - Alpha-Ketoglutarate Dehydrogenase

ALDH - Aldehyde Dehydrogenase

cAMP-PKA - Cyclic Adenosine Monophosphate - Protein Kinase A

CD38 - Cluster of Differentiation 38 (NAD+ glycohydrolase)

COMPLEX I - NADH:Ubiquinone Oxidoreductase

DOPAL - 3,4-Dihydroxyphenylacetaldehyde

eATP - Extracellular Adenosine Triphosphate

FAD - Flavin Adenine Dinucleotide

GDH - Glutamate Dehydrogenase

GHB - gamma-Hydroxybutyrate

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

PDH - Pyruvate Dehydrogenase

P5P - Pyridoxal 5-Phosphate

Q - Ubiquinone

QH₂ - Ubiquinol

ROS - Reactive Oxygen Species

RNS - Reactive Nitrogen Species

TCA - Tricitric Acid

THP - Tetrahydropapaveroline

TPP - Thiamine Pyrophosphate

Zn²⁺ - Zinc Ion