MICROBIOME DERIVED ACETALDEHYDE

→ Inhibits ALDH2, ALDH1A1/1A2
→ Consumes NAD+ → ↑ NADH
→ Creates toxic aldehydes (e.g. DOPAL, 5-HIAL)
→ ↑ THP, ↑ Endogenous Morphine → μ-Opioid Receptor Activation → ↓ cAMP-PKA Signalling
→ Promotes histamine release (mast cell, basophil activation; exacerbated by NAD^+/P5P/Zn depletion)
→ Inhibits glucose uptake, methylation
→ Promotes cholesterol biosynthesis (inhibited ALDH2)

COFACTOR DEPLETION SPIRAL

→ ↓ NAD^+:NADH
→ ↓ B1 (TPP) → ↓ PDH, ↓ TCA, ↓ Transketolase, ↓ SLC19A1
→ ↓ B2 (FMN/FAD) → ↓ ETC Complex I/II, GSH Reductase, MTHFR, [..]
→ ↓ B3 (NAD^+) → ↓ Sirtuins, ↓ PARPs
→ ↓ B6 (P5P) → ↓ Neurotransmitter synthesis, ↓ KYNU, ↓ GAD
→ ↓ Zn^{2+} → ↓ ALP, PK, PNPO, DAO, PH, RBP4 function
→ ↓ Vitamin C → ↓ Iron reduction, ↓ Dopamine β-hydroxylase, ↑ Oxidative stress, ↓ PH
→ ↓ CoA (from B5) → ↓ Acetyl-CoA availability
→ ([..], see Figure 7)

HISTAMINE DYSREGULATION

→ ↑ Histamine (DAO, ALDH, P5P, Zn depletion)
→ H2R (liver): ↑ cAMP-PKA → initial ↑ glycogenolysis
→ H1R (muscle): ↑ Ca^{2+} → ↑ glycogen synthesis
→ Chronic exposure: H1/H2 receptor desensitisation, impaired cAMP-PKA/PLC signalling
→ Progressive failure of glycogen mobilisation (liver, muscle)
→ ↑ Hypoglycaemia risk, worsened fatigue, adrenergic symptoms

LIVER GLYCOGEN HOMEOSTASIS

→ Acute: Epinephrine, glucagon, histamine (H2R) drive cAMP-PKA → ↑ glycogen phosphorylase → ↑ glycogenolysis (liver glucose output preserved)
→ Requires intact cAMP-PKA and NAD+, P5P, Zn, Mn for gluconeogenesis
→ Chronic acetaldehyde, endogenous morphine, receptor desensitisation: ↓ cAMP-PKA responsiveness
→ Glycogen stores become depleted/inaccessible; gluconeogenesis impaired (low NAD^+, Zn, P5P)
→ Liver cannot buffer stress, fasting, or hypoglycaemia → paradoxical crashes, adrenergic symptoms
→ Feedback: Hypoglycaemia triggers further catecholamine/histamine release, worsening the collapse spiral

RETINOID METABOLISM BLOCKADE

→ ALDH1A1/1A2 inhibition → ↓ Retinal → ↓ Retinoic Acid (RA)
→ ↓ RAR/RXR signalling → ↓ epithelial barrier genes, ↓ T-reg differentiation, ↑ Th17 skew
→ ↓ STRA6-mediated retinol uptake (Zn^{2+}-dependent)
→ ↓ RBP4 transport (Zn^{2+}-dependent)
→ ↓ NAD^+ → ↓ ADH/RDH activity → impaired retinol oxidation to retinal
→ Immune shift + neurodevelopment disruption

IMMUNOMETABOLIC DISRUPTION

→ ↑ IFN-gamma → ↑ IDO1/TDO
→ Tryptophan → Kynurenine → Blocked downstream by: ↓ P5P (↓ KYNU), ↑ ROS (↓ 3-HAO)
→ ↓ NAD^+ synthesis via de novo path
→ ↑ QA / 3-HK → neurotoxicity
→ ↓ Serotonin → mood dysregulation
→ (Acetaldehyde, IFN →) ↑ ROS inhibits mitochondrial Complex I (NADH dehydrogenase) → exacerbates NADH accumulation
→ ↑ NADH pool → ↑ NADP transhydrogenase → ↑ NADPH (mitochondria)
→ ↑ ROS (loop)

ENERGY FAILURE

→ ↓ cAMP-PKA → ↓ NMNAT ("NAD+ Trap"), ↓ TH (Low dopamine, trap regulator), ↓ Mitochondrial biogenesis
→ ↓ Glycolysis → ↓ PRPP → ↓ Nucleotide synthesis
→ ↓ PPP → ↓ NADPH (cytosol)
→ ↑ NADH:NAD^+, impaired ETC
→ ↓ Acetyl-CoA → Histone hypoacetylation, ↓ Krebs cycle flux
→ Liver: Glycogenolysis and gluconeogenesis fail (low cAMP, receptor desensitisation, vitamin/metal depletion)
→ Muscle: Impaired glycogen mobilisation (H1R/Ca^{2+} and adrenergic cross-talk blunted)
→ Systemic: Hypoglycaemia, exercise intolerance, metabolic rigidity

OUTPUT STATES

→ Immune hyperactivation + cytokine excess
→ Neurotransmitter collapse (↓ DA, NE, 5-HT, GABA)
→ Redox failure → ↑ ROS/RNS
→ Mitochondrial hypometabolism
→ Impaired repair + barrier leakage (gut, BBB, skin)
→ Behavioural rigidity, fatigue, sensory overload
→ Mineral depletion via cytokine mediated hepcidin cascade

KEY FEEDBACK LOOPS

- Acetaldehyde → ALDH block → NAD^+ depletion → vitamin trap → immune + metabolic collapse
- Acetaldehyde/histamine loop: NAD^+/P5P/Zn loss → histamine excess → short-term glycogen mobilisation, long-term collapse as cAMP-PKA axis fails
- Endogenous morphine → μOR → ↓ cAMP-PKA → suppresses NMNAT / NAD+ biosynthesis, all energy and repair pathways
- ↓ RA + ↓ Zn^{2+} → compromised immunity, epithelial fragility, failed neuroplasticity

Figure 10. Pathway Diagram: Simplified block diagram of acetaldehyde-mediated metabolic cascade

ME/CFS: Correcting Chronic Mitochondrial Dysfunction

Author: Joshua Leisk ©2025, [DRAFT / INCOMPLETE - may contain errors] v0.42

3-HAO - 3-Hydroxyanthranilate 3,4-Dioxygenase
3-HK - 3-Hydroxykynurenine
5-HIAL - 5-Hydroxyindoleacetaldehyde
5-HT - Serotonin (5-Hydroxytryptamine)
ADH - Alcohol Dehydrogenase
ALDH - Aldehyde Dehydrogenase
ALP - Alkaline Phosphatase
B1, B2, B3, B5, B6 - B Vitamins 1 (Thiamine), 2 (Riboflavin), 3 (Niacin), 5 (Pantothenic Acid), 6 (Pyridoxine)
BBB - Blood-Brain Barrier
Ca - Calcium
cAMP-PKA - Cyclic Adenosine Monophosphate - Protein Kinase A
CoA - Coenzyme A
DA - Dopamine
DAO - Diamine Oxidase
DOPAL - 3,4-Dihydroxyphenylacetaldehyde
ETC - Electron Transport Chain
FAD - Flavin Adenine Dinucleotide
FMN - Flavin Mononucleotide
GABA - Gamma-Aminobutyric Acid
GAD - Glutamate Decarboxylase
GSH - Glutathione
H1R / H2R - Histamine Receptor 1 / 2
IDO1 / TDO - Indoleamine 2,3-Dioxygenase 1 / Tryptophan 2,3-Dioxygenase
IFN-γ - Interferon gamma
KYNU - Kynureninase
NAD+ / NADH - Nicotinamide Adenine Dinucleotide (oxidised / reduced)
NADP - Nicotinamide Adenine Dinucleotide Phosphate
NADPH - Nicotinamide Adenine Dinucleotide Phosphate (reduced form)
NE - Norepinephrine
NMNAT - Nicotinamide Mononucleotide Adenylyltransferase
P5P - Pyridoxal 5'-Phosphate (active vitamin B6)
PARPs - Poly(ADP-ribose) Polymerases
PDH - Pyruvate Dehydrogenase
PH - Prolyl Hydroxylase
PK - Pyridoxal Kinase
PLC - Phospholipase C
PNPO - Pyridoxine 5'-Phosphate Oxidase
PPP - Pentose Phosphate Pathway
PRPP - Phosphoribosyl Pyrophosphate
QA - Quinolinic Acid
RA - Retinoic Acid
RAR - Retinoic Acid Receptor
RDH - Retinol Dehydrogenase
RBP4 - Retinol Binding Protein 4
RXR - Retinoid X Receptor
STRA6 - Stimulated by Retinoic Acid 6 (retinol transporter)
TCA - Tricarboxylic Acid Cycle (Krebs Cycle)
THP - Tetrahydropapaveroline
TPP - Thiamine Pyrophosphate (active vitamin B1)
Zn - Zinc
μOR / μ-Opioid Receptor - Mu Opioid Receptor