STAGE 1: Early Compensation (Epinephrine-Driven)

Stage 1 Description

1. Chronic epinephrine/adrenaline (stress, inflammation, hypoglycaemia)
2. ↑ cAMP-PKA in hepatocytes → ↑ glycogen phosphorylase, ↓ glycogen synthase → ↑ glycogenolysis
and ↑ gluconeogenesis (if mineral cofactors, NAD+, P5P are sufficient)

'Wired but functional' – normal or high glucose, adrenergic symptoms

Transition: Ongoing acetaldehyde burden, NAD+ depletion, histamine surge, morphine accumulation, β2AR/H2R desensitisation

HISTAMINE DYSREGULATION

1. ↑ Histamine (ALDH, P5P, Zn depletion)
2. H2R (liver): ↑ cAMP-PKA → initial ↑ glycogenolysis
3. H1R (muscle): ↑ Ca2+ → ↑ glycogen synthesis
4. Chronic exposure: H1/H2R desensitisation, impaired cAMP-PKA/PLC signalling
5. Progressive failure of glycogen mobilisation (liver, muscle)
6. ↑ hypoglycaemia risk, worsened fatigue, adrenergic symptoms

STAGE 2: Trap Onset (Compensation Failure)

Stage 2 Description

1. μ-Opioid receptor (endogenous morphine/THP) suppresses cAMP-PKA (↓ NMNAT, [..])
2. β2AR/H2R desensitisation/internalisation
3. ↓ Glycogenolysis, ↓ hepatic & muscle glucose output, blunted stress response
4. Gluconeogenesis impaired (low NAD+, P5P)

Glucose crash, exercise intolerance, paradoxical hypoglycaemia

Transition: Further collapse of cAMP-PKA, NAD+ synthesis, ALDH, mitochondrial flux, histamine receptor failure

STAGE 3: Full Collapse (Hypometabolic, Glycogen Failure)

Stage 3 Description

1. cAMP-PKA tone persistently low, even with stress or histamine signals
2. Glycogen depleted/inaccessible, liver & muscle cannot buffer glucose swings
3. Gluconeogenesis minimal
4. Profound fatigue, neuroglycopenia, adrenergic instability ('wired but can't mount response')

Feedback: hypoglycaemia → further stress hormone activation → worsens collapse

OUTPUT: Systemic Collapse

1. Immune hyperactivation, cytokine excess
2. Neurotransmitter collapse (↓ DA, NE, 5-HT, GABA)
3. Redox failure, ↑ ROS/RNS
4. Mitochondrial hypometabolism
5. Barrier leakage (gut, BBB, skin)
6. Cytokines → hepcidin → ↓ mineral status
7. Fatigue, sensory overload, cognitive failure
8. Reflex cAMP-PKA hypersensitivity to beta-adrenergic signalling, impaired liver glucose homeostasis

Key Feedbacks

1. Acetaldehyde → ALDH/NAD+/Zn/P5P/histamine collapse → immune & metabolic collapse
2. Morphine → mu-OR → ↓ cAMP-PKA → suppression of NAD+ synthesis, energy/repair
3. ↓ RA/Zn → immune/epithelial/neuroplasticity failure
4. Glucose crash/hypoglycaemia worsens all

3-HAO - 3-Hydroxyanthranilate 3,4-Dioxygenase
3-HK - 3-Hydroxykynurenine
5-HIAL - 5-Hydroxyindoleacetaldehyde
5-HT - Serotonin
ADH/RDH - Alcohol Dehydrogenase / Retinol Dehydrogenase
ALDH - Aldehyde Dehydrogenase
ALP - Alkaline Phosphatase
BBB - Blood-Brain Barrier
Ca^{2+} - Calcium ion
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
H2R / H1R - Histamine Receptor 2 / 1
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
PARPs - Poly(ADP-ribose) Polymerases
PDH - Pyruvate Dehydrogenase
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/RXR - Retinoic Acid Receptor / Retinoid X Receptor
RBP4 - Retinol Binding Protein 4
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

Figure 11. Pathway Diagram: Simplified overview of acetaldehyde-mediated disease progression.

ME/CFS: Correcting Chronic Mitochondrial Dysfunction

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