Detailed Description
Endogenous morphine signalling and sympathetic drive pull the cyclic adenosine monophosphate-protein kinase A axis, abbreviated cAMP-PKA, in opposite directions, yet over time they converge on the same transcription factor, the cAMP response-element binding protein (CREB). Activation of μ-opioid receptors engages the inhibitory G-protein family (Gi), suppresses adenylyl cyclase, lowers basal cAMP and reduces PKA activity. In compensation, neurons and hepatocytes increase expression of certain cyclase isoforms, of the catalytic sub-unit of PKA and of CREB itself, gradually restoring throughput despite continuing receptor inhibition. Sympathetic tone, arriving through β-adrenergic stimulatory G-proteins (Gs), pushes cAMP the other way; each burst of epinephrine now strikes tissue that has already amplified its signalling sensitivity.

The result is a primed system that appears stable while endogenous morphine persists yet stores potential energy in surplus adenylyl cyclase and poised PKA. Once phosphorylated, CREB drives transcription of more cyclase, more PKA and, in neurons, of tyrosine hydroxylase, thereby increasing catecholamine synthesis. Hepatocytes receiving the same molecular message phosphorylate glycogen phosphorylase, switch off glycogen synthase and release glucose immediately. When endogenous morphine production falters or is abruptly blocked, the Gi restraint disappears, cAMP rises rapidly and the accumulated PKA is unleashed within minutes. Sympathetic drive, already high because mitochondrial efficiency is low and hepatic glycogen scarce, now meets no opposition; adrenaline surges, blood glucose oscillates and extra-synaptic N-methyl-D-aspartate (NMDA) receptors become fully phosphorylated, lowering their activation threshold and producing the familiar excitotoxic features of withdrawal.

5-HT$_1$ - Serotonin 1 Receptor Family
A$_1$ - Adenosine A1 Receptor
α$_2$-AR - Alpha-2 Adrenergic Receptor
AC - Adenylyl Cyclase
Akt - Protein Kinase B
ALDH - Aldehyde Dehydrogenase
AMPA - α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid
AR - Androgen Receptor
β-AR - Beta-Adrenergic Receptor
BHB - Beta-hydroxybutyrate
Ca^{2+}/CaM - Calcium/Calmodulin Complex
cAMP - Cyclic Adenosine Monophosphate
CB$_1$ - Cannabinoid CB1 Receptor
cGMP - Cyclic Guanosine Monophosphate
CREB - cAMP Response Element-Binding Protein
D$_2$-like - Dopamine D2-like Receptor Family
DHEA - Dehydroepiandrosterone
DOPAL - 3,4-Dihydroxyphenylacetaldehyde
ERK - Extracellular Signal-Regulated Kinase
GABA - Gamma-Aminobutyric Acid
Gβγ - G protein βγ Sub-units
Gi - Inhibitory G-alpha Sub-unit
GPR109A - Nicotinic Acid Receptor
GPER1 - G protein-Coupled Oestradiol Receptor 1 (GPR30)
GRK3 - G Protein-Coupled Receptor Kinase 3
Gs - Stimulatory G-alpha Sub-unit
GSK3β - Glycogen-Synthase-Kinase-3β
HCAR2 - Hydroxycarboxylic Acid Receptor 2
HMG-CoA - 3-Hydroxy-3-Methylglutaryl-Coenzyme A
HSD3β - Hydroxy-Delta-5-Steroid Dehydrogenase 3β
ICER - Inducible cAMP Early Repressor
IR - Insulin Receptor
mGluR - Metabotropic Glutamate Receptor
MOR - Mu-Opioid Receptor
mPR - Membrane Progesterone Receptor
MT1 - Melatonin Receptor 1
NAD$^+$ - Nicotinamide Adenine Dinucleotide
NO - Nitric Oxide
NOS - Nitric Oxide Synthase (coupled)
NMDA - N-Methyl D-Aspartic Acid
NMNAT - Nicotinamide Mononucleotide Adenylyltransferase
PDE - Phosphodiesterase
PEM - Post Exertional Malaise
PEPCK - Phosphoenolpyruvate Carboxykinase
PFK2 - 6-Phosphofructo-2-Kinase
PI3K - Phosphoinositide 3-Kinase
PKA - Protein Kinase A
PKG - cGMP-dependent Protein Kinase
POTS - Postural Orthostatic Tachycardia Syndrome
PregS - Pregnenolone Sulphate
R - Receptor
RNS - Reactive Nitrogen Species
ROS - Reactive Oxygen Species
RSK - Ribosomal S6 Kinase
RTK - Receptor Tyrosine Kinase
sGC - Soluble Guanylyl Cyclase
THDOC - Tetrahydrodeoxycorticosterone
TRPM3 - Transient Receptor Potential Melastatin 3

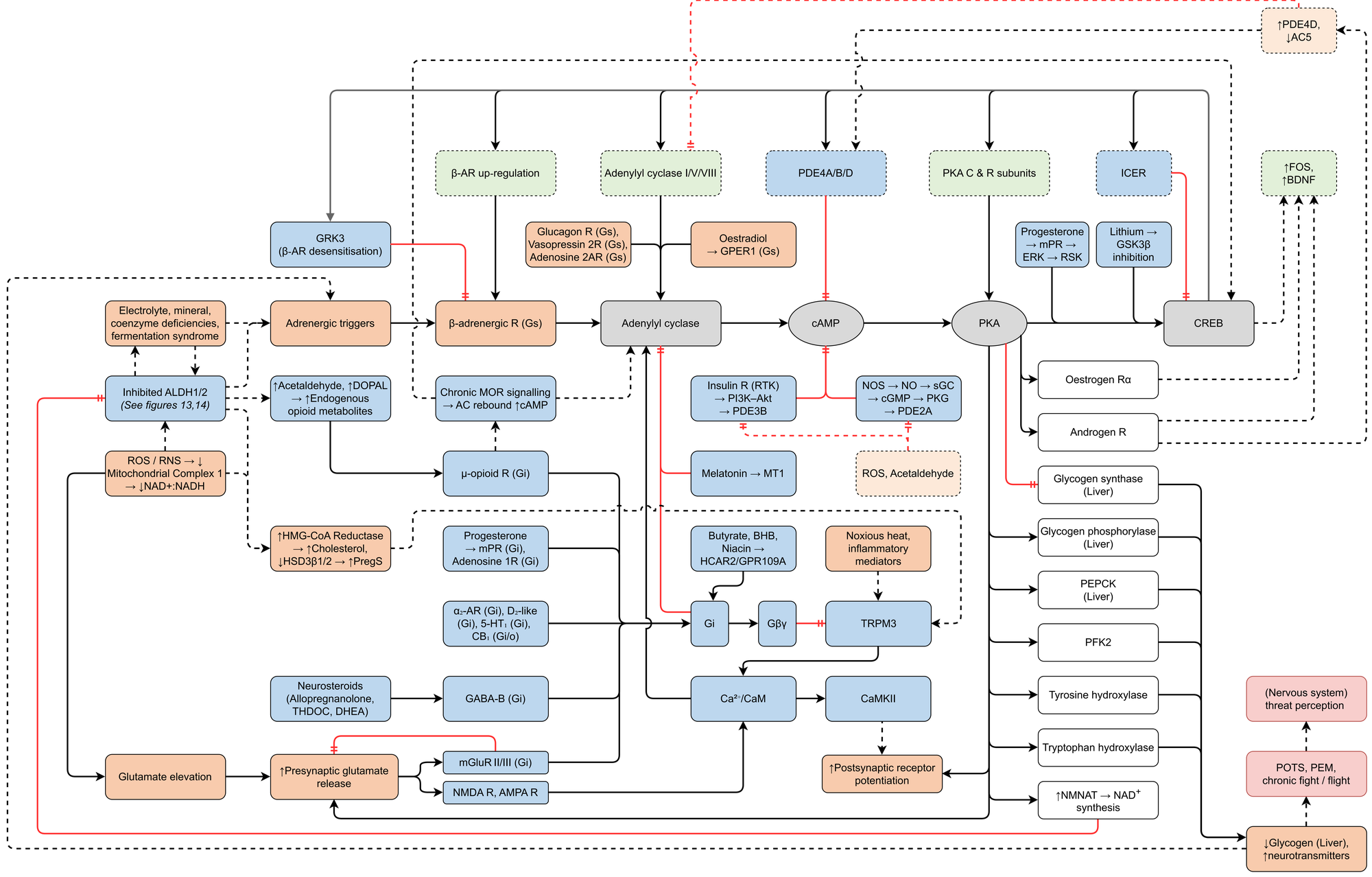

Figure 18. Pathway Diagram: Simplified overview of cAMP-PKA alterations in fermentation syndrome

ME/CFS: Correcting Chronic Mitochondrial Dysfunction

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Connector Key:
Promoted
Inhibited
Abbreviated