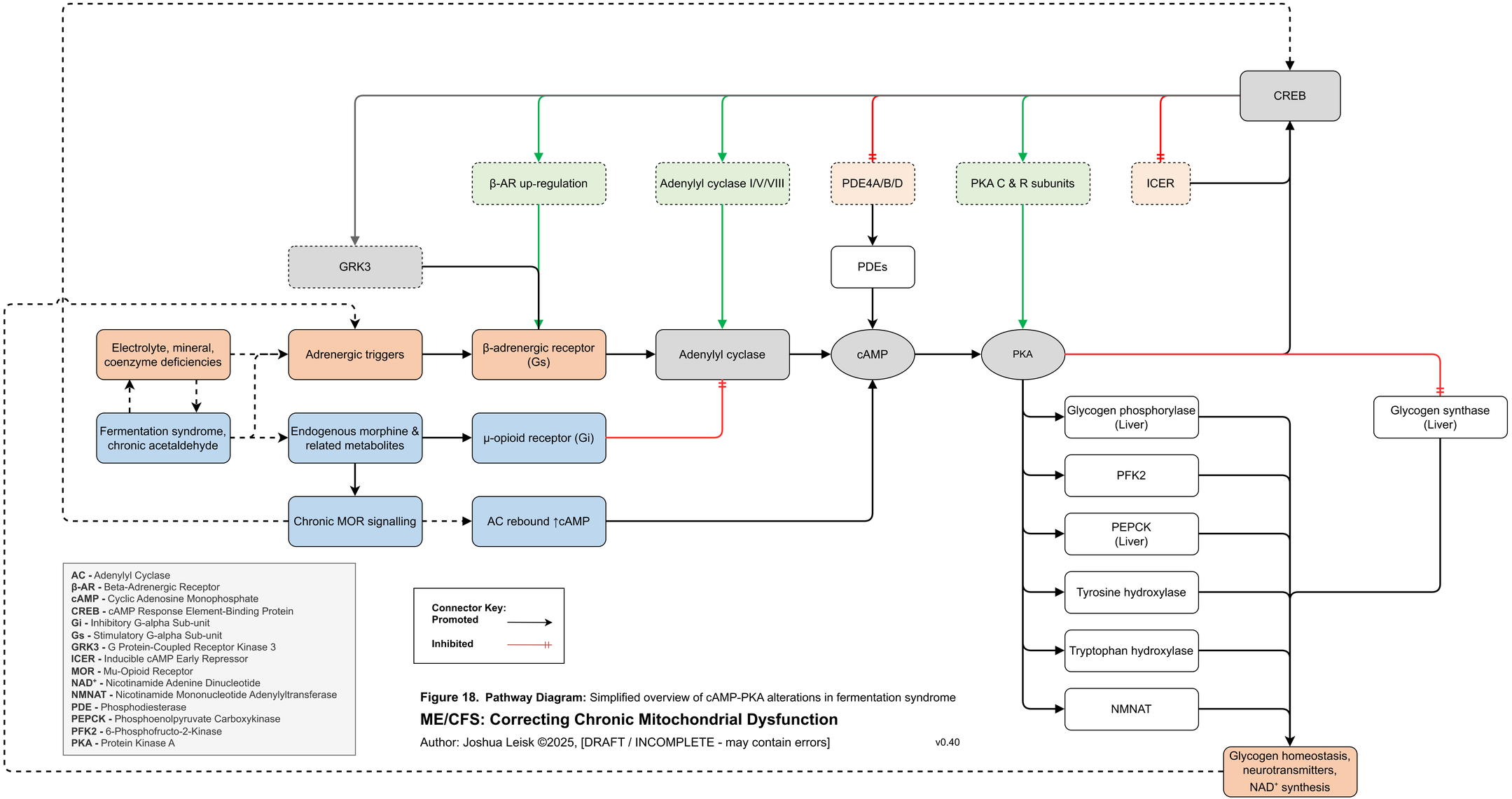
Detailed Description:

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.



AC - Adenylyl Cyclase
β-AR - Beta-Adrenergic Receptor
cAMP - Cyclic Adenosine Monophosphate
CREB - cAMP Response Element-Binding Protein
Gi - Inhibitory G-alpha Sub-unit
Gs - Stimulatory G-alpha Sub-unit
GRK3 - G Protein-Coupled Receptor Kinase 3
ICER - Inducible cAMP Early Repressor
MOR - Mu-Opioid Receptor
NAD⁺ - Nicotinamide Adenine Dinucleotide
NMNAT - Nicotinamide Mononucleotide Adenylyltransferase
PDE - Phosphodiesterase
PEPCK - Phosphoenolpyruvate Carboxykinase
PFK2 - 6-Phosphofructo-2-Kinase
PKA - Protein Kinase A

Connector Key:
Promoted →
Inhibited —||

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

ME/CFS: Correcting Chronic Mitochondrial Dysfunction

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