

**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  $\mu$ -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  $\beta$ -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  
**Akt** - Protein Kinase B  
**AR** - Androgen Receptor  
 **$\beta$ -AR** - Beta-Adrenergic Receptor  
**cAMP** - Cyclic Adenosine Monophosphate  
**cGMP** - Cyclic Guanosine Monophosphate  
**CREB** - cAMP Response Element-Binding Protein  
**ERK** - Extracellular Signal-Regulated Kinase  
**Gi** - Inhibitory G-alpha Sub-unit  
**GPER1** - G protein-Coupled Oestradiol Receptor 1 (GPR30)  
**GRK3** - G Protein-Coupled Receptor Kinase 3  
**Gs** - Stimulatory G-alpha Sub-unit  
**GSK3 $\beta$**  - Glycogen-Synthase-Kinase-3 $\beta$   
**ICER** - Inducible cAMP Early Repressor  
**IR** - Insulin Receptor  
**mGluR** - Metabotropic Glutamate Receptor  
**MOR** - Mu-Opioid Receptor  
**mPR** - Membrane Progesterone Receptor  
**NAD<sup>+</sup>** - Nicotinamide Adenine Dinucleotide  
**NO** - Nitric Oxide  
**NOS** - Nitric Oxide Synthase (coupled)  
**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  
**R** - Receptor  
**ROS** - Reactive Oxygen Species  
**RSK** - Ribosomal S6 Kinase  
**RTK** - Receptor Tyrosine Kinase  
**sGC** - Soluble Guanylyl Cyclase

