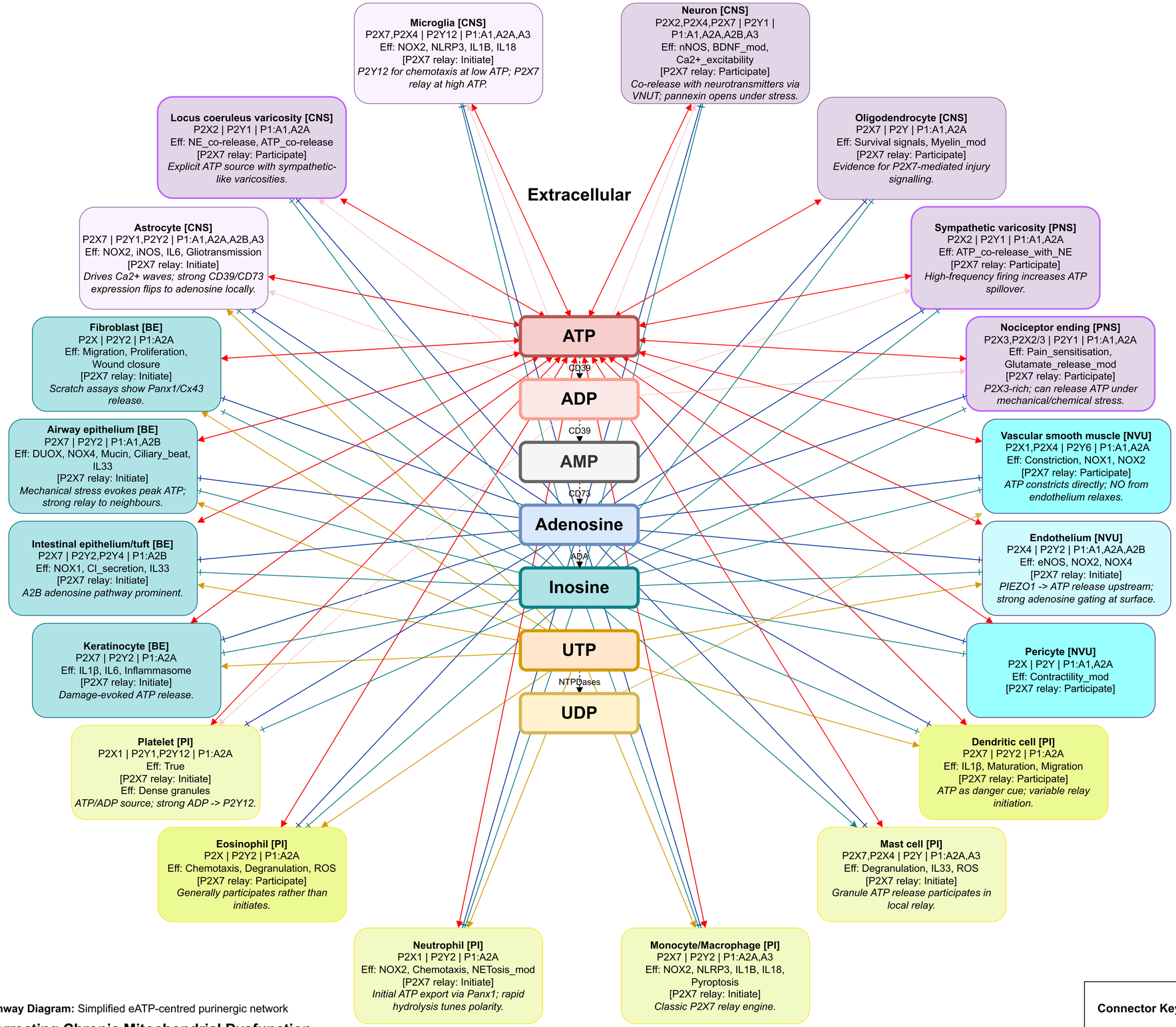

Figure 19. Pathway Diagram: Simplified eATP-centred purinergic network

ME/CFS: Correcting Chronic Mitochondrial Dysfunction

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

v0.45

Connector Key:

Promoter →
Inhibitor —|

_mod - Modulation
A1 - Adenosine A1 Receptor
A2A - Adenosine A2A Receptor
A2B - Adenosine A2B Receptor
A3 - Adenosine A3 Receptor
ADA - Adenosine Deaminase
ADP - Adenosine Diphosphate
AMP - Adenosine Monophosphate
ATP - Adenosine Triphosphate
BDNF - Brain-Derived Neurotrophic Factor
BE - Barrier Epithelia
Ca2+ - Calcium Ion
CD39 - Ectonucleoside Triphosphate Diphosphohydrolase 1
CD73 - 5′-nucleotidase, Ecto
Cl - Chloride
CNS - Central Nervous System
Cx43 - Connexin 43 (gene: GJA1)
Eff - Effector
eNOS - Endothelial Nitric Oxide Synthase
IL - Interleukin
IMP - Inosine Monophosphate
iNOS - Inducible Nitric Oxide Synthase
NE - Norepinephrine
NLRP3 - NLR Family Pyrin Domain Containing 3
nNOS - Neuronal Nitric Oxide Synthase
NO - Nitric Oxide
NOX - NADPH Oxidase
NVU - Neurovascular Unit
Panx1 - Pannexin-1
P2X - P2X Purinergic Receptor Family
P2Y - P2Y Purinergic Receptor Family
Panx1 - Pannexin-1 (gene: PANX1)
PI - Peripheral Immune
PNS - Peripheral Nervous System
ROS - Reactive Oxygen Species
UDP - Uridine Diphosphate
UTP - Uridine Triphosphate

Legend
Node types: nucleotides/nucleoside (central) and cells (external).
Connector styles: solid = receptor signalling; dashed = enzymatic reaction.
Explicit ATP sources relevant to hyper-arousal are highlighted with purple outlines (locus coeruleus varicosities [CNS], sympathetic varicosities [PNS], and nociceptor endings [PNS]).

In-node tags
Compartment tag in brackets match node colour groups, e.g. [CNS], [PNS], [NVU], [BE], [PI].
Receptors are listed inline: “P2X… | P2Y… | P1:…”.
“Eff:” lists key effectors (eg. NOX2, eNOS).

Description
A representation of how extracellular ATP (eATP) and related nucleotides shape signalling across nervous, vascular, epithelial, and immune cells.

Ligand binding
(Activation)
ATP → P2X channels; ATP also drives P2Y2 and, where present, P2Y11.
ADP → P2Y1, P2Y12, P2Y13.
UTP → P2Y2, P2Y4.
UDP → P2Y6.
(Dampening)
Adenosine, inosine → P1 receptors (A1, A2A, A2B, A3).

Dynamics
Low-moderate nucleotide levels favour P2Y/P1 signalling. High local extracellular ATP activates cells with P2X7 receptors, causing Ca2+ influx and K+ efflux, assembly of NOX with ROS production, NLRP3 activation, cytokine processing, and secondary ATP release that feeds back to the extracellular ATP node (red). This is normally a per-compartment cascade.

("[Relay: Initiate]" indicates cells can start a high-ATP P2X7 loop; [Relay: Participate] indicates cells can reliably engage once a loop is running.)

ATP is also hydrolysed to ADP and AMP by CD39, AMP to adenosine by CD73, adenosine to inosine by ADA; in parallel UTP is hydrolysed to UDP by NTPDases. *Inosine is also produced from IMP, via de novo synthesis from glutamine, or the purine nucleotide cycle (muscle, post-exertion).*

Adenosine and inosine agonise P1 receptors. P1 connectors are blue / aqua and represent context-dependent dampening or modulation of the relay *(functionally antagonistic to the red signalling pathways)*.

Notes, scope and limits
Receptor lists are dominant rather than exhaustive. Effector listings are intentionally brief to preserve readability. Local ectonucleotidase expression, tissue geometry, and species/assay context will shift the balance between relay and resolution.

Evidence in rodents also shows that psychological or restraint stress rapidly elevates extracellular ATP in hippocampus and prefrontal cortex, as detected by in vivo microdialysis. Blocking P2X7 reduces the associated cytokine surge. Stress also increases hemichannel opening in hippocampal astrocytes, microglia and, with chronic exposure, neurons. Inhibiting Cx43/Panx1 reduces stress-evoked ATP and glutamate release. Together, this supports an ATP-mediated feed-forward loop during hyper-arousal.