

TRPV1 as a Central Point of Convergence in Post-Spike Syndrome Pathomechanisms of PEM/PENE, POTS, MCAS, and SFN, and a Phase-Based Therapeutic Framework

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ABSTRACT

Post-spike syndromes following SARS-CoV-2 infection and modRNA vaccination—post-exertional malaise/neuroimmune exhaustion (PEM/PENE), postural orthostatic tachycardia syndrome (POTS), mast cell activation syndrome (MCAS), and small fiber neuropathy (SFN)—share a common molecular axis of convergence despite their divergent clinical presentations. We propose that the transient receptor potential vanilloid 1 (TRPV1) channel acts as a central sentinel receptor that detects the spike protein as an exogenous signal and translates it, via three parallel axes—an ion axis ($\text{Ca}^{2+}/\text{Na}^{+}$), a glutamate/N-methyl-D-aspartate (NMDA) axis, and a neuropeptide/immune axis (substance P/neurokinin-1 receptor)—into a shared mitochondrial dysfunction. Central to this model is the interplay between TRPV1-mediated $\text{Ca}^{2+}/\text{Na}^{+}$ influx, compensatory SERCA and Ca^{2+} -activated potassium channel activity, mitochondrial Ca^{2+} uptake via the mitochondrial calcium uniporter (MCU) and the mitochondrial sodium–calcium exchanger (NCLX), and a downstream glutamatergic amplification loop converging on the NMDA receptor. Building on this mechanistic model, we develop a phase-based therapeutic framework (mast cell foundation, neuronal and synaptic braking, neuroinflammatory resolution), in which pharmacological, nutritional, and lifestyle interventions are mapped onto the corresponding steps of the cascade. The model generates testable mechanistic predictions and is conceptually situated within the exposome surveillance hypothesis.

Keywords

TRPV1, Post-spike syndrome, post-exertional malaise, PENE, POTS, Mast cell activation syndrome, small fiber neuropathy, Substance P, NMDA receptor, Mitochondrial dysfunction, Exposome, GRABSR.

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Abbreviations

2-AG, 2-arachidonoylglycerol; AKT, protein kinase B; ATP, adenosine triphosphate; BK, big-conductance Ca^{2+} -activated potassium channel; CB2, cannabinoid receptor type 2; CDC, Centers for Disease Control and Prevention; CGRP, calcitonin gene-related peptide; COX-2, cyclooxygenase-2; CSF, cerebrospinal

fluid; DAO, diamine oxidase; DNCG, sodium cromoglicate (disodium cromoglycate); FGFR-3, fibroblast growth factor receptor 3; GABA, gamma-aminobutyric acid; GPCR, G-protein-coupled receptor; GRABSR, Guided Restoration of Adaptive Biological Self-Regulation; ICC, International Consensus Criteria; IENFD, intraepidermal nerve fibre density; IL-1 β , interleukin-1

beta; IL-6, interleukin-6; IOM, Institute of Medicine; KCa, Ca²⁺-activated potassium channel; Kv7, voltage-gated potassium channel subfamily KQT member 7; LDN, low-dose naltrexone; MAMs, mitochondria-associated membranes; MAPR, mitochondrial ATP production rate; MCAS, mast cell activation syndrome; MCU, mitochondrial calcium uniporter; modRNA, modified ribonucleic acid; mPTP, mitochondrial permeability transition pore; MRGPRX2, Mas-related G-protein-coupled receptor member X2; NCLX, mitochondrial sodium–calcium exchanger; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NGF, nerve growth factor; NK1R, neurokinin-1 receptor; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; NMDA, N-methyl-D-aspartate; OXPHOS, oxidative phosphorylation; PEA, palmitoylethanolamide; PEM, post-exertional malaise; PENE, post-exertional neuroimmune exhaustion; PI3K, phosphoinositide 3-kinase; POTS, postural orthostatic tachycardia syndrome; PPAR-α, peroxisome proliferator-activated receptor alpha; ROS, reactive oxygen species; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SERCA, sarco/endoplasmic reticulum Ca²⁺-ATPase; SFN, small fiber neuropathy; SP, substance P; Src, proto-oncogene tyrosine-protein kinase Src; TCA, tricarboxylic acid; TLR4, Toll-like receptor 4; TNF-α, tumour necrosis factor alpha; TRPV1, transient receptor potential vanilloid 1; VGCCs, voltage-gated calcium channels; ΔΨm, mitochondrial membrane potential.

Introduction and Terminology

Post-spike syndromes following SARS-CoV-2 infection and modRNA vaccination comprise clinically heterogeneous but mechanistically closely interconnected entities: post-exertional malaise/neuroimmune exhaustion (PEM/PENE), postural orthostatic tachycardia syndrome (POTS), mast cell activation syndrome (MCAS), and small fiber neuropathy (SFN).

PEM (IOM/CDC terminology) and PENE (Canadian Consensus Criteria/ICC terminology) describe, at their core, the same phenomenon—a delayed, disproportionate, multisystem worsening of symptoms following exertion, with impaired recovery—and are treated here as a single pathophysiological entity.

The TRPV1-centred cascade presented below can be conceptually situated within the exposome surveillance hypothesis, which posits that environmental information (here: the spike protein as an exogenous signal) is translated by distributed sentinel

receptors into adaptive neuroimmunological regulation, and that its progressive maladaptation constitutes a shared systemic basis for chronic multisystem disease [1].

PEM/PENE arises as a self-perpetuating loop of mitochondrial dysfunction, immune activation, and neuroinflammation: a reduced mitochondrial ATP production rate (MAPR) and impaired OXPHOS efficiency synergistically activate the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), translating metabolic stress into systemic inflammation [2,3].

POTS results from four overlapping mechanisms—hypovolaemia, autonomic neuropathy, a hyperadrenergic state, and deconditioning—with long-COVID POTS additionally showing a well-documented autoimmune component: autoantibodies against G-protein-coupled receptors (α-/β-adrenoceptor, angiotensin II, and muscarinic receptors) disturb the balance of neuronal and vascular regulation [4].

MCAS is most directly linked to the spike protein itself: the spike protein induces the in-vitro release of chymase and tryptase from human mast cells via the Src/PI3K/AKT/Ca²⁺ signalling cascade [5], with residual spike protein forming chymase complexes that enhance cellular entry [6].

SFN arises through four proposed mechanisms—autoimmune reaction, direct viral invasion, systemic inflammation, and “unmasking” of subclinical pre-existing damage [7]—and is closely linked clinically to PEM (92% comorbidity in a case–control study) and POTS [8].

All four mechanisms converge on a shared upstream event: persistent spike protein acting as a continuous antigenic/danger signal.

TRPV1 as a Central Molecular Hub

The transient receptor potential vanilloid 1 (TRPV1) channel translates the spike signal into all four syndromes:

- **SFN:** SARS-CoV-2 and its S1 spike protein induce TRPV1 translocation from the nucleus to the plasma membrane, with consequent Ca²⁺-mediated axonal degeneration; pharmacological TRPV1 inhibition (capsazepine) causally prevents this neuronal injury [9].

Differentiating the Four Syndromes

Syndrome	Primary target compartment	Principal mechanism	Specific marker
PEM/PENE	Mitochondria/energy metabolism	ATP deficit → NLRP3/NF-κB → systemic inflammation	↓ MAPR, ↓ OXPHOS, CSF metabolomics
POTS	Autonomic nervous system/vasculature	GPCR autoantibodies (α-/β-adrenergic, muscarinic)	Anti-GPCR titres
MCAS	Mast cell	Direct spike-mediated degranulation (Src/PI3K/AKT/Ca ²⁺)	Tryptase, chymase, residual spike
SFN	Small nerve fibres	Autoimmune (anti-GPCR/FGFR-3) + direct invasion + unmasking	IENFD (skin biopsy), GPCR autoantibodies

Table abbreviations: ATP, adenosine triphosphate; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; MAPR, mitochondrial ATP production rate; OXPHOS, oxidative phosphorylation; CSF, cerebrospinal fluid; GPCR, G-protein-coupled receptor; Src, proto-oncogene tyrosine-protein kinase Src; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; FGFR-3, fibroblast growth factor receptor 3; IENFD, intraepidermal nerve fibre density.

- **MCAS:** activated TRPV1⁺ neurons release substance P, which directly triggers mast cell degranulation via MRGPRX2 [10]—a self-amplifying loop that converges with spike-induced direct mast cell activation [5].
- **POTS:** indirectly, via neurogenic vasodilation (calcitonin gene-related peptide, CGRP, release) and sensitisation of vagal/cardiac afferents [11].
- **PEM/PENE:** TRPV1-mediated Ca²⁺ influx burdens mitochondrial buffering capacity and culminates in oxidative stress and inflammasome activation [12].

Substance P and the Neurokinin-1 Receptor

Substance P (SP) is released both from TRPV1⁺ nerve terminals and, non-neuronally, from mast cells, macrophages, and dendritic cells, and binds the neurokinin-1 receptor (NK1R).

A recent study found elevated neuropeptide/cytokine levels with NK1R-mediated neuroinflammation in long-COVID patients with neuropsychological sequelae; computational docking identified aprepitant as a particularly high-affinity NK1R antagonist [13]. Notably, older cerebrospinal fluid studies in non-post-viral ME/CFS found substance P levels within the normal range (in contrast to fibromyalgia) [14]—suggesting that SP/NK1R upregulation is specifically associated with post-viral/post-spike pathogenesis, which provides a pharmacological rationale for aprepitant use in this population.

NK1R also contributes to early fever-generating signalling pathways and to mast cell maturation—NK1R blockade has been shown experimentally to directly suppress mast cell maturation, independent of neuronal SP release [15].

The Complete Ion and Signalling Cascade

TRPV1 as a Polymodal Trigger: Coupled Ca²⁺ and Na⁺ Influx

TRPV1 is a non-selective cation channel that, upon activation, conducts both Ca²⁺ and Na⁺, thereby generating a depolarising receptor potential [12]. The local Ca²⁺ concentration in the immediate vicinity of the channel exceeds the global cytosolic concentration by more than an order of magnitude (submembrane nanodomains >10 μM) [16].

First Line of Compensation: SERCA and Ca²⁺-Activated Potassium Channels

SERCA (sarco/endoplasmic reticulum Ca²⁺-ATPase) pumps cytosolic Ca²⁺ back into the ER lumen in an ATP-consuming manner—the first energetic burden of the cascade, even before mitochondria become involved.

Ca²⁺-activated potassium channels (KCa, chiefly BK/KCa1.1) are directly and functionally coupled to TRPV1 at the plasma membrane: local Ca²⁺ influx activates BK channels within sub-millisecond timescales [16]. The resulting K⁺-mediated membrane hyperpolarisation acts as a negative feedback mechanism; Kv7 channels additionally dampen TRPV1-triggered Ca²⁺ responses pharmacologically by up to 60% [17].

Mitochondrial Ca²⁺ Uptake: Physiological Benefit and Pathological Tipping Point

Via ER-mitochondria contact sites (mitochondria-associated membranes, MAMs), Ca²⁺ reaches the vicinity of the mitochondrial calcium uniporter (MCU)—a direct functional coupling between TRPV1 and this mitochondrial Ca²⁺-shuttling machinery has been demonstrated [12]. In moderate amounts, this Ca²⁺ uptake activates tricarboxylic acid (TCA) cycle dehydrogenases and increases ATP production according to demand [18].

Mitochondria also possess their own Ca²⁺-activated potassium channel (mitoBKCa) in the inner membrane, whose activation produces a mild, protective depolarisation of ΔΨ_m, thereby limiting the driving force for MCU-mediated uptake and reactive oxygen species (ROS) production—analogue to the mitoKATP mechanism of ischaemic preconditioning [19].

Under chronic TRPV1 overactivation, this buffering capacity becomes exhausted: Ca²⁺ overload induces cyclophilin D-regulated opening of the mitochondrial permeability transition pore (mPTP), with collapse of ΔΨ_m, uncoupling of oxidative phosphorylation (OXPHOS), ROS escalation [20], and—if sufficiently severe—cytochrome c release with consequent apoptosis or necrosis [21]. This pattern of mitochondrial dysfunction is consistent with findings reported directly in ME/CFS patients [3].

The Independent Na⁺ Axis

TRPV1-mediated Na⁺ influx contributes to pathology via several independent mechanisms:

- **Amplification:** Na⁺-driven depolarisation opens voltage-gated Ca²⁺ channels (VGCCs), increasing total Ca²⁺ influx.
- **Modulation of mitochondrial Ca²⁺ retention:** the mitochondrial Na⁺/Ca²⁺ exchanger (NCLX) is the principal route of Ca²⁺ extrusion from the matrix; the energy available for this exchange depends directly on the transmembrane Na⁺ concentration gradients [22].
- **An independent energy crisis:** elevated mitochondrial Na⁺-independent of Ca²⁺ overload - directly inhibits oxidative phosphorylation and the tricarboxylic acid cycle via NCLX, with consequent ATP deficiency and failure of the Na⁺/K⁺-ATPase [23].
- **Additional ATP expenditure:** Na⁺ extrusion via the Na⁺/K⁺-ATPase places further strain on an already compromised mitochondrial ATP supply.

The Glutamatergic Amplification Loop: Convergence on the NMDA Receptor

TRPV1 activation directly triggers an increase in action-potential-independent vesicular glutamate release. The sustained phase of this release depends on mitochondrial Ca²⁺ uptake and release—mitochondria act as a time-delayed Ca²⁺ reservoir that decouples and prolongs excitatory signalling beyond its original trigger [24]. The NMDA receptor is unblocked through the convergence of three mechanisms: TRPV1-mediated Na⁺ depolarisation, substance P/CGRP release, and the sustained glutamate release itself [25].

Once unblocked, the NMDA receptor constitutes a third, highly permeable Ca^{2+} source that converges on the same mitochondrial endpoint: mitochondrial depolarisation, cytochrome c release, and caspase-3/9 activation [21].

Figure: The Overall Cascade and Therapeutic Targets

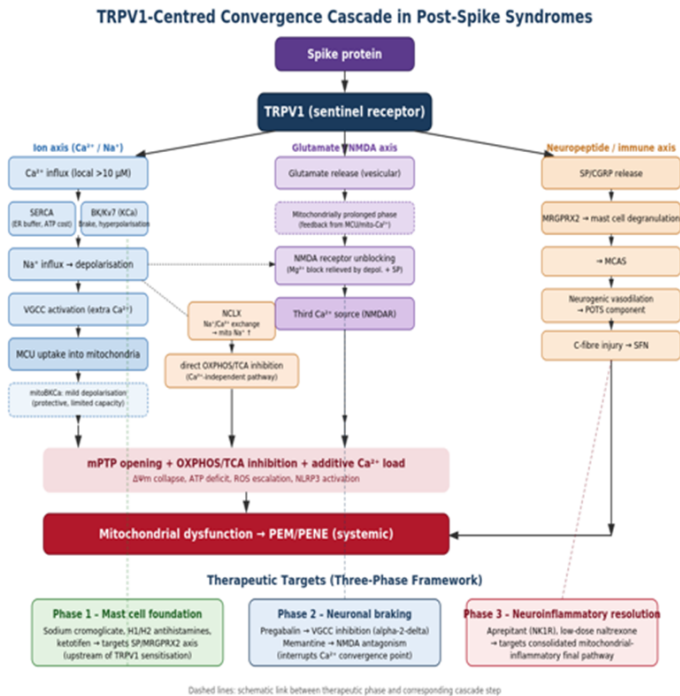


Figure 1: TRPV1-centred convergence cascade in post-spike syndromes. Beginning with the spike protein, TRPV1 activates three parallel axes (ion, glutamate/NMDA, and neuropeptide/immune) that converge on a shared mitochondrial dysfunction and account for the four target syndromes (PEM/PENE, POTS, MCAS, SFN). The three therapeutic phases target distinct, empirically motivated points within the cascade.

Synthesis: The Overall Model

Spike protein → TRPV1 activation → (a) direct Ca^{2+} influx + (b) Na^+ -driven depolarisation → SERCA-/KCa-mediated first-line compensation → mitochondrial Ca^{2+} uptake via MCU (physiological, up to capacity) → under chronic load: mPTP opening (Ca^{2+} axis) AND direct NCLX-mediated OXPHOS/TCA inhibition (Na^+ axis) → ATP deficit → in parallel: TRPV1-triggered, mitochondrially prolonged glutamate release → NMDA receptor unblocking → third Ca^{2+} source → additional mitochondrial burden → cytochrome c release, caspase activation → mitochondrial dysfunction as the shared final common pathway of PEM/PENE, with a parallel neuropeptidergic branch to MCAS, POTS, and SFN.

Critically, several elements of this cascade—particularly the mitochondrial prolongation of glutamate release and Na^+ -mediated disruption of mitochondrial bioenergetics—are structurally self-reinforcing and can therefore persist independently of the original trigger. This provides a mechanistic explanation for the clinically observed chronification of symptoms and their apparent

decoupling from the inciting exposure.

Therapeutic Implications (Three-Phase Framework)

- Phase 1 – Mast cell foundation** (sodium cromoglicate, H1/H2 antihistamines, diamine oxidase supplementation, ketotifen): targets the upstream trigger of TRPV1 sensitisation via the SP/MRGPRX2/mast cell axis.
- Phase 2 – Neuronal and synaptic braking** (pregabalin, memantine): pregabalin reduces secondary VGCC-mediated Ca^{2+} influx via the $\alpha 2\delta$ subunit of voltage-gated Ca^{2+} channels; memantine, as an NMDA antagonist, specifically interrupts the point of convergence of TRPV1 depolarisation, substance P release, and mitochondrially prolonged glutamate release.
- Phase 3 – Neuroinflammatory resolution** (memantine continued, low-dose naltrexone, aprepitant): targets the consolidated, already chronified mitochondrial-inflammatory final common pathway; NK1R antagonism via aprepitant is pharmacologically justified by the specifically post-viral upregulation of the SP/NK1R axis.

Mechanisms of Action of the Therapeutic Agents (Phases 1–3)

Phase 1 – Mast Cell Foundation

Sodium cromoglicate (DNCG): A classical mast cell stabiliser whose molecular target most likely lies in inhibition of a chloride channel essential for mast cell degranulation, which regulates membrane stability and the Ca^{2+} influx required for exocytosis [26]. Owing to minimal systemic absorption, it acts almost exclusively locally (gut mucosa, conjunctivae, airways) and thus primarily on the mucosal mast cell population. It targets the terminal execution step of mast cell degranulation, irrespective of whether this is triggered by direct spike activation or via the SP–MRGPRX2 axis.

H1 antihistamines: Competitive H1 receptor antagonists that block histamine-mediated vasodilation, vascular permeability, pruritus, and bronchoconstriction. Purely receptor-blocking, not degranulation-inhibiting.

H2 antihistamines: Block H2 receptors, which mediate not only gastric acid secretion but also endothelial/cardiac histaminergic effects (flushing, vasodilation, gastrointestinal symptoms). Combined H1/H2 blockade is synergistic, as both receptor subtypes cover complementary histamine-mediated effects.

Diamine oxidase (DAO) supplementation: Supplies exogenous DAO enzyme, which degrades dietary histamine within the gut lumen before absorption. It does not act on endogenous mast cell degranulation but reduces the exogenous contribution to the systemic histamine load, potentially bringing the total burden below the individual symptom threshold.

Ketotifen: A dual mechanism of action—non-competitive H1 antagonism and mast cell stabilisation via blockade of the Ca^{2+} influx critical for degranulation, together with prevention of the cAMP decline required for terminal vesicle fusion [27]. This dual action

explains the additional reduction in TNF- α and other chemokines observed in a randomised controlled trial in fibromyalgia [28]. A specific TRPV1-modulating effect is not robustly supported by the literature; the observed effect is adequately explained by the combined Ca²⁺ channel/H1 action at the mast cell itself.

Phase 2 – Neuronal and Synaptic Braking

Pregabalin: Binds with high affinity to the $\alpha 2\delta$ -1 subunit of voltage-gated Ca²⁺ channels (VGCCs), regulating their trafficking efficiency to the presynaptic membrane rather than directly blocking the channel pore [29]. The net effect is reduced presynaptic Ca²⁺ entry upon depolarisation and reduced release of excitatory neurotransmitters (glutamate, substance P). Pregabalin thus acts precisely at the VGCC amplification node activated by TRPV1-Na⁺-driven depolarisation, simultaneously reducing both the additional mitochondrial Ca²⁺ load and the downstream glutamate/SP release that feeds NMDA unblocking and the MRGPRX2 mast cell axis—a central bottleneck blocker between the ion axis and the glutamate/neuropeptide axis.

Phase 3 – Neuroinflammatory Resolution

Memantine: A low-to-moderate affinity, voltage-dependent, uncompetitive NMDA receptor antagonist. As a use-dependent “open-channel blocker”, it blocks the channel pore only when the receptor is already pathologically (tonically, subthreshold) activated, while physiological phasic synaptic transmission is largely preserved owing to fast off-kinetics [30]. It specifically interrupts the third Ca²⁺ source of the cascade model—the NMDA-mediated additional Ca²⁺ load arising from the convergence of TRPV1 depolarisation, substance P release, and mitochondrially prolonged glutamate release.

Low-dose naltrexone (LDN): Acts via two independent mechanisms. First, transient opioid receptor blockade with a consequent rebound increase in endogenous opioids (endorphins, enkephalins). Second—more relevant to neuroinflammation—antagonism of Toll-like receptor 4 (TLR4) on microglia and astrocytes, independent of the opioid receptor; TLR4 activation drives the release of pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6) and reactive oxygen species, which LDN directly dampens [31]. It thereby targets the consolidated, chronified final common pathway—mPTP-/NCLX-triggered NLRP3/NF- κ B activation—at the glial/systemic inflammatory level, complementary to neuronal NMDA blockade.

Aprepitant: A high-affinity NK1R antagonist [13] that interrupts substance P signalling at three points: (1) NK1R-mediated neuroinflammation associated with long-COVID-specific neuropsychological sequelae [13]; (2) NK1R-mediated mast cell maturation and activation, independent of neuronal SP release [15]; (3) SP-triggered systemic cytokine release. Its positioning in Phase 3 is justified by the fact that the specifically post-viral upregulated SP/NK1R axis represents an already consolidated, chronified component that should be targeted only after the acute mast cell (Phase 1) and Ca²⁺ overload (Phase 2) burdens have been reduced.

Phase-Specific Roles of Diet, Micronutrients, Lifestyle, and Hormetic Stimuli

Phase 1 – Mast Cell Foundation

Diet: A low-histamine diet reduces exogenous, dietary histamine load (aged/fermented foods, alcohol, certain fish species, aged cheese), thereby relieving a histamine clearance system already overwhelmed by spike-triggered mast cell degranulation. Not all patients require a strict diet—indication should be symptom-guided.

Micronutrients: - **Quercetin:** In an *in-vitro* study on human mast cells, quercetin was more effective than cromolyn itself at inhibiting substance-P-induced histamine release [32]—a direct target within the SP-MRGPRX2 axis of our cascade model. Limitation: very low oral bioavailability (~1%); enteric-coated formulations are preferred. - **Vitamin C:** a cofactor (with copper and vitamin B6) for the DAO enzyme, and additionally contributes to direct histamine degradation [33]. - **Luteolin:** a structurally related flavonoid with, in some respects, even more potent mast cell stabilisation and additional neuroprotective properties [32]. - **Palmitoylethanolamide (PEA):** see 10.3—owing to its specific substance-P-antagonising action at the mast cell, also retrospectively relevant to Phase 1, particularly in patients with a persistent SP-MCAS axis.

Lifestyle: Avoidance of known triggers (thermal extremes as direct TRPV1 stimuli, alcohol, acute psychological stress), sleep hygiene, and targeted stress reduction—an 8-week stress management programme was shown in a randomised controlled trial in Hashimoto’s thyroiditis to reduce thyroglobulin antibodies via the HPA axis [34], a mechanism that may translate to the SP-driven MCAS axis.

Hormetic stimuli: Deliberately withheld. As long as the mast cell axis remains unstabilised, additional physiological stimuli (heat, cold, exertion) risk further amplifying TRPV1 activation rather than eliciting an adaptive response. Phase 1 serves to reduce adaptive debt, not to build adaptive capacity.

Phase 2 – Neuronal and Synaptic Braking

Diet: a magnesium-rich diet (leafy greens, nuts, whole grains, cocoa), with adequate protein intake for neurotransmitter precursors.

Micronutrients: - **Magnesium** – the central micronutrient of this phase: magnesium physiologically acts as an endogenous, voltage-dependent NMDA channel blocker—it sits structurally within the channel pore and prevents precisely the excessive Ca²⁺/glutamate influx that memantine mimics pharmacologically [35]. Under intracellular magnesium deficiency, this “plug” is removed, leading to uncontrolled NMDA-mediated Ca²⁺ influx—magnesium and memantine thus act synergistically at the same molecular site. Magnesium is additionally a natural Ca²⁺ channel blocker (complementing pregabalin’s $\alpha 2\delta$ action) and an essential cofactor for GABA synthesis, tricarboxylic acid cycle enzymes,

and the Mg-ATP complex. - **Vitamins B6/B12/folate:** cofactors for neurotransmitter synthesis and homocysteine metabolism. - **Taurine:** acts primarily as an agonist at the inhibitory glycine receptor and at the GABA-A receptor. A clearly dampening effect directly at the NMDA receptor is inconsistently supported in the literature and should not be presented as an established mechanism of action.

On the role of glycine

Glycine acts in the central nervous system at two pharmacologically distinct binding sites. At the separate, strychnine-sensitive glycine receptor (GlyR, predominantly spinal cord/brainstem), it acts inhibitorily. At the strychnine-insensitive glycine-B binding site on the GluN1 subunit of the NMDA receptor, however, glycine is an obligatory co-agonist [36]—the NMDA receptor cannot open at this site without glycine binding, even in the presence of glutamate. Glycine is thus a prerequisite for, not a brake on, NMDA activation, and is therefore not suited as an NMDA-dampening micronutrient in this phase. Any potential benefit lies at most in its sleep-supporting effect (lowering core body temperature) and would accordingly be classified under lifestyle/sleep optimisation.

Lifestyle: Strict pacing within the individual energy envelope—explicitly excluding graded exercise, given the PEM issue. Sleep optimisation, vagal-/breathing-technique-based interventions.

Hormetic stimuli: A cautious, non-exertional introduction is justifiable: HRV biofeedback/paced breathing (shown to be safe in controlled studies in long-COVID patients meeting ME/CFS criteria, with significant improvements in fatigue and autonomic symptoms) [37], and possibly very low-dose thermal therapy [38]—always with PEM screening prior to any dose escalation.

Phase 3 – Neuroinflammatory Resolution

Diet: An anti-inflammatory, Mediterranean-style diet with adequate high-quality fats—omega-3 fatty acids and phospholipids serve not only inflammatory modulation but also as structural mitochondrial membrane building blocks.

Micronutrients: - **Coenzyme Q10** (preferably in the reduced ubiquinol form): a central electron transport chain cofactor, acting synergistically with magnesium, D-ribose, and acetyl-L-carnitine. - **Acetyl-L-carnitine:** supports mitochondrial fatty acid transport (β -oxidation). - **Alpha-lipoic acid:** a mitochondrial cofactor with additional antioxidant activity, directly reducing the ROS burden arising from mPTP opening. - **D-ribose:** provides substrate for nucleotide/ATP resynthesis. - **NAD⁺ precursors** (nicotinamide riboside/NMN): support mitochondrial biogenesis. - **B-vitamin complex** (particularly B1/thiamine): an essential cofactor for tricarboxylic acid cycle enzymes.

Palmitoylethanolamide (PEA)

An endogenous fatty acid amide (the ALIAmide concept—“autacoid local injury antagonism”) acting primarily via the nuclear receptor peroxisome proliferator-activated receptor alpha (PPAR- α). Two mechanisms are directly relevant to Phase

3. First, PEA has been shown to antagonise substance-P-induced mast cell histamine release by stimulating diacylglycerol lipase activity, thereby increasing endogenous 2-arachidonoylglycerol (2-AG), which in turn exerts cannabinoid receptor type 2 (CB2)-mediated mast cell stabilisation [39]—a direct target within the SP-MRGPRX2 axis. Second, PEA increases CB2 receptor expression on microglia via PPAR- α activation, promoting a phenotypic shift from reactive/pro-inflammatory to homeostatic/phagocytic, with suppression of NGF, COX-2, TNF- α , and iNOS release [40]. PEA thus complements low-dose naltrexone as a second, independent modulator of microglial activity: LDN acts via TLR4 antagonism, PEA via PPAR- α /CB2—two independent signalling pathways converging on the same target [41].

The literature also describes a so-called entourage effect of PEA, whereby PPAR- α activation by PEA may potentiate anandamide-mediated TRPV1 sensitisation. At first glance, this appears to conflict with the present model, in which TRPV1 activation is pathogenic. However, the net effect of PEA across clinical and preclinical studies is consistently anti-inflammatory/analgesic—most plausibly explained by the PPAR- α -mediated transcriptional effects (mast cell stabilisation, CB2 upregulation) outweighing the TRPV1 entourage effect on balance, possibly also via capsaicin-like TRPV1 desensitisation following initial potentiation.

Lifestyle: Only at this stage, if at all, cautious, strictly PEM-guided activity escalation; circadian optimisation as a basis for nocturnal repair/clearance processes.

Hormetic stimuli: Here, the full range of previously discussed, evidence-based candidates becomes relevant: continued thermal therapy (Waon protocol with slow progression) [38], continued HRV biofeedback [37], possibly non-invasive vagus nerve stimulation, and possibly photobiomodulation—always embedded within a PEM safety framework with a symptom diary as a stopping criterion, as outlined in principle 8 of the Guided Restoration of Adaptive Biological Self-Regulation (GRABSR) framework [1].

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