Palmitoylethanolamide (PEA) acts as a **"self-repair molecule"** in the nervous system, uniquely combining neuroprotective, anti-inflammatory, and neurorestorative actions to address the root causes of peripheral neuropathy.

Mechanisms of Nerve Repair

Unlike standard treatments that only mask pain, PEA intervenes in the biological alterations of nerve tissue to promote healing:

- **Structural Restoration**: PEA treatment has been shown to restore morphological continuity in damaged nerves, increasing **myelin sheath thickness** and **axonal diameter**.
- **Schwann Cell & Axonal Support**: It promotes the survival and proper functioning of neurons by upregulating **Brain-Derived Neurotrophic Factor (BDNF)**, which is critical for neural repair and reversing the abnormal synaptic remodeling that occurs in chronic pain.
- **Prevention of Degeneration**: PEA inhibits **apoptosis** (programmed cell death) in nerve tissues, specifically reducing pro-apoptotic proteins like BAX while increasing protective proteins like Bcl-2.
- **Myelinated Fiber Enhancement**: Recent 2025 clinical evidence indicates that PEA can improve the function of **myelinated nerve fibers**, which are essential for proper nerve signaling and are often damaged in conditions like chemotherapy-induced neuropathy.

Addressing the Root Cause (Neuroinflammation)

PEA repairs the neural environment by controlling the "inflammatory cascade" that otherwise prevents healing:

- **Mast Cell Stabilization**: It stabilizes mast cells in the periphery, preventing the release of pro-inflammatory mediators that cause endoneural edema and fiber degeneration.
- **Glial Homeostasis**: In the central nervous system, PEA modulates **microglia and astrocytes**, reducing the neuroinflammation that maintains chronic pain states and leads to secondary nerve damage.
- **PPAR-α Activation**: This primary pathway switches off gene networks responsible for producing inflammatory cytokines and chemokines, creating a favorable microenvironment for nerve regeneration.

Therapeutic Synergy

PEA is increasingly used in combination with other agents to accelerate repair:

- **PEA + Acetyl L-Carnitine (ALC)**: Clinical studies show this combination significantly improves healing and functional recovery in sciatic nerve and carpal tunnel injuries.
- **PEA + Antioxidants**: Formulations combining PEA with Alpha-Lipoic Acid (ALA) or superoxide dismutase (SOD) provide comprehensive protection by reducing oxidative stress alongside PEA's anti-inflammatory actions.
- **Enhanced Formulations**: Recent developments like **Equisetum-PEA** or **micronized PEA (PEA-m)** improve absorption and target delivery, allowing the molecule to reach damaged tissues more effectively.