

Based on the provided sources, **no**, Palmitoylethanolamide (PEA) is not the only endogenous (produced within the body) neuroregenerative compound. While PEA is highlighted as a "pro-homeostatic" lipid signaling molecule produced by microglia and mast cells to resolve inflammation and support myelin repair 1, 2, the sources identify several other endogenous compounds produced by animals (and often found in plants) that actively promote nerve regeneration and repair.

The following endogenous compounds are identified in the texts as having neuroregenerative or neuroprotective properties:

## 1. Spermidine

- **Nature:** A natural polyamine found in ribosomes and living tissues of animals, as well as in plants like wheat germ, soybeans, and mushrooms 3.
- **Regenerative Function:** It acts as a "debris clearance specialist" by inducing **autophagy** (a cellular recycling process). It is critical for clearing cellular rubble (such as broken cell walls and spilled chemicals) at the injury site, allowing the new axon to advance 4.
- **Evidence:** In models of chronic constriction injury, spermidine reversed neuronal degeneration and fibrosis, significantly improving nerve conduction velocity 5, 6.

## 2. Neurotrophic Factors (Proteins)

The body naturally produces several proteins specifically designed to maintain and repair neurons.

- **Nerve Growth Factor (NGF):** Essential for the development and maintenance of peripheral neurons. Reduced availability of NGF contributes to diabetic neuropathy 7. Enhancing NGF levels promotes recovery of peripheral nerve damage 8, 9.
- **Brain-Derived Neurotrophic Factor (BDNF):** A neuronal growth factor important for the repair of the peripheral nervous system 10.
- **Insulin-like Growth Factor-1 (IGF-1):** An endogenous protein that maintains neuronal survival and synaptic function. Restoring neuronal IGF-1 expression suppresses neuroinflammation and prevents neuropathy 11, 9.
- **Prosaposin:** A precursor protein (to saposins A, B, C, and D) identified as a neurotrophic factor that facilitates nerve regeneration in vivo 12.

## 3. Specialized Pro-Resolving Mediators (Lipids)

- **Neuroprotectin D1 (NPD1):** A lipid mediator derived from docosahexaenoic acid (DHA). It facilitates neurite outgrowth and protects against sensory neuron degeneration and neuropathic pain 13, 14.
- **Resolvins (D1/D2):** Endogenous anti-inflammatory mediators found in human serum that help block glial reaction and improve nerve conduction 15.

## 4. Hormones and Neurosteroids

- **Progesterone and Allopregnanolone:** Endogenous steroids that act as physiological regulators in the peripheral nervous system. They have been shown to reverse electrophysiological impairments, reduce demyelination, and promote motor recovery in neuropathy models 16, 17, 18.
- **Erythropoietin (EPO):** While known for red blood cell production, endogenous EPO transcription in glial cells (Schwann cells) prevents axonal degeneration 19.
- **Melatonin:** An endogenous hormone that exerts neuroprotective effects, potentially by reducing oxidative stress and preserving nerve structure 20, 21.

## 5. Gasotransmitters and Antioxidants

- **Hydrogen Sulfide (H<sub>2</sub>S):** Produced endogenously by enzymes like cystathione-β-synthase (CBS). It has neuroprotective effects, modulating astrocyte activation and reducing pro-inflammatory cytokines in diabetic neuropathy 22, 23.
- **Glutathione:** An endogenous antioxidant essential for protecting nerves from oxidative stress. Its depletion is linked to the severity of neuropathy 24, 25.

### Summary Table of Endogenous Regenerative Agents

Compound, Type, Primary Regenerative Mechanism, Source

PEA, Fatty Acid Amide, Modulates inflammation (PPAR-α); supports myelin repair., "1, 26"

Spermidine, Polyamine, Induces autophagy to clear cellular debris., "4, 5"

NGF / BDNF, Protein, Promotes neuron survival and axon growth., "7, 10"

IGF-1, Protein, Maintains synaptic function; suppresses neuroinflammation., 11

Neuroprotectin D1, Lipid, Facilitates neurite outgrowth; prevents degeneration., 13

Progesterone, Steroid, Promotes myelination and reverses electrophysiological deficits., 16

Erythropoietin, Glycoprotein, Prevents axonal degeneration via glial cell signaling., 19