

# Abstract

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## Lipid-mediated cell signaling protects against injury and neurodegeneration.

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**BACKGROUND:** Deficiency in docosahexaenoic acid (DHA) is associated with impaired visual and neurological development, cognitive decline, macular degeneration, and other neurodegenerative diseases. DHA is concentrated in phospholipids of the brain and retina, with photoreceptor cells having the highest DHA content of all cell membranes.

**DISCUSSION:** The discovery that **neuroprotectin D1 (NPD1)**; 10R, 17S-dihydroxy-docosa-4Z,7Z,11E,13E,15Z,19Z-hexaenoic acid) is a bioactive mediator of DHA sheds light on the biological importance of this fatty acid. In oxidative stress-challenged human retinal pigment epithelial (RPE) cells, human brain cells, or brain ischemia-reperfusion, NPD1 synthesis is enhanced as a response for sustaining homeostasis. Thus, neurotrophins, Abeta peptide (Abeta)42, calcium ionophore A23187, interleukin-1beta (IL-1beta), or DHA supply enhances NPD1 synthesis. NPD1, in turn, upregulates the antiapoptotic proteins of the Bcl-2 family and decreases the expression of proapoptotic Bcl-2 family members. In human neural cells, DHA attenuates Abeta42 secretion, resulting in concomitant formation of NPD1. NPD1 repressed Abeta42-triggered activation of proinflammatory genes and upregulated the antiapoptotic genes encoding Bcl-2, Bcl-xl, and Bfl-1(A1) in human brain cells in culture.

**CONCLUSIONS:** Overall, **NPD1 signaling regulates brain and retinal cell survival via the induction of antiapoptotic and neuroprotective gene-expression programs that suppress Abeta42-induced neurotoxicity and other forms of cell injury. These in turn support homeostasis during brain and retinal aging, counteract inflammatory signaling, and downregulate events that support the initiation and progression of neurodegenerative disease.**

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