Docosahexaenoic Acid (DHA) in Stroke, Alzheimer’s Disease, and Blinding Retinal Degenerations: Coping with Neuroinflammation and Sustaining Cell Survival

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The significance of the selective enrichment in omega-3 essential fatty acids (docosahexaenoyl – DHA- chains of membrane phospholipids, 22C and 6 double bonds) in the nervous system (e.g. photoreceptors, synaptic membranes) has remained, until recently, incompletely understood. While studying mechanisms of cell survival in neurodegenerations, we contributed to the discovery of a docosanoid synthesized from DHA by 15-lipoxygenase-1, which we dubbed neuroprotectin D1 (NPD1,10R,17S-dihydroxy-docosa-4Z,7Z,11E,13E,15E,19Z hexaenoic acid). This mediator is a docosanoid because it is derived from a 22C precursor (DHA), unlike eicosanoids, which are derived from the 20 C arachidonic acid family member of essential fatty acids not enriched in the nervous system. We found that NPD1 is promptly made in response to oxidative stress and brain ischemia-reperfusion, and in the presence of neurotrophins. NPD1 is neuroprotective in experimental brain damage, oxidative-stressed retinal pigment epithelial (RPE) cells, and in human brain cells exposed to amyloid-β peptide. Thus we envision NPD1 as a protective sentinel, one of the very first defenses activated when cell homeostasis is threatened by neurodegenerations. We provide here recent experimental examples that highlight the specificity and potency of NPD1 spanning beneficial bioactivity during initiation and early progression of neurodegenerations: 1) Photoreceptors renew membrane disks containing the phototransduction apparatus and DHA intermittently via shedding of their tips and phagocytosis by retinal pigment epithelial (RPE) cells. At the same time, new membrane disks are made at the base of the outer segments; their length remains constant and cell integrity is maintained remarkably unchanged throughout many decades. This outcome occurs in spite of the fact that the photoreceptors are in an oxidative stress-prone environment (light, high O2 consumption, high polyunsaturated fatty acid fluxes, etc). We show that phagocytosis of photoreceptor disks promotes via NPD1 synthesis specific refractoriness to oxidative stress-induced apoptosis in RPE cells, which in turn fosters homeostatic photoreceptor cell integrity. Disruptions of the sentinel role of NPD1 in photoreceptor renewal may participate in macular degeneration and other retinal degenerations leading to blindness. 2) In brain ischemia-reperfusion, DHA (i.v.) one hour after two hours of middle cerebral artery occlusion (MCAO) leads to penumbra protection with an extended time window of protection (up to five hours) and with concomitant NPD1 synthesis. Anti-apoptotic BCL-2 family of proteins availability is positively modulated by NPD1, whereas pro-apoptotic BCL-2 proteins are negatively regulated, as is the arrival of leukocytes due to neurovascular unit breakdown. 3) NPD1 is drastically reduced in CA1 areas from Alzheimer’s patients. Thus we have explored the significance of NPD1 in cellular models that recapitulate part of the Alzheimer’s pathology. Human neurons and astrocytes challenged by amyloid-β or by overexpressing APPsw (double Swedish mutation) show that NPD1 downregulates amyloidogenic processing of amyloid-β precursor protein, switches off pro-inflammatory gene...