Unesterified docosahexaenoic acid promotes photoreceptors survival activating a retinoid orphan receptor

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Docosahexaenoic acid (DHA), the major omega-3 polyunsaturated fatty acid in the retina, promotes the survival of rat retina photoreceptors (PR) during early development in vitro and upon oxidative stress by activating the ERK/MAPK signaling pathway. We investigated if DHA activates this pathway by direct activation of tyrosine kinase receptors (TRK) or of retinoid nuclear receptors (RXR). Using retinal neuronal cultures we determined that DHA prevented PR apoptosis at early culture times in spite of the presence of a TRK inhibitor (K252a), implying TRK are not involved in its effects. On the contrary, RXR antagonists (HX531 or PA452) inhibited DHA protection during early development in vitro and upon paraquat and H2O2-induced apoptosis. Moreover, RXR agonists (HX630 or PA024) decreased photoreceptors apoptosis in H2O2-treated neuronal cultures, as we previously showed for DHA. To evaluate whether DHA has to be released from phospholipids to exert its protective effect, DHA-supplemented cultures were treated with a phospholipase A2 inhibitor (BEL) prior to H2O2 treatment; BEL addition blocked DHA protection on PR upon oxidative stress. These results suggest a new pathway for DHA actions in PR: it is first released from phospholipids and then activates RXR to promote PR survival.

Keywords: Photoreceptors, RXR, Docosahexaenoic acid