Neuroprotective Mechanism of Docosahexaenoic Acid in Genotoxic Stress Evoked by DNA Akylation

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Poly(ADP-ribose) polymerase-1 (PARP-1) is a nuclear enzyme strongly activated in response to oxidative and genotoxic stress DNA damage. Its over-activation leads to the energy crisis and neuronal death. The last data indicated that the enzymatic product of PARP-1, poly(ADP-ribose) (PAR) acts as a signaling molecule and plays significant role in nucleus/mitochondria cross-talk. PAR translocated to mitochondria can be involved in mitochondrial permeability and apoptosis inducing factor (AIF) release. These processes can lead to DNA condensation and fragmentation and to the cell death. Last data showed that docosahexaenoic acid (DHA), a major dietary ω-3 long-chain polyunsaturated fatty acid, plays potent protective actions. In the present study we evaluated the effect of genotoxic stress evoked by alkylating agent (N-methyl-N'-nitro-N-nitrosoguanidine, MNNG), on mitochondria function, AIF level and its translocation into nucleus in HT22 hippocampal neuronal cells. The neuroprotective action of DHA comparing to the PARP-1 inhibitors was explored. The genotoxic stress evoked by MNNG enhanced the level of PAR in time and concentration dependent manner with concomitant significant decreased of AIF protein level in mitochondria. In these conditions massive cells death was observed. DHA as well as both PARP-1 inhibitors (3-AB and PJ34), protected most of HT22 cells against AIF translocation into nucleus and against death. These inhibitors express ameliorating effect on MNNG induced the up-regulation of anti-apoptotic Bcl-xL gene expression. Our data show that docosahexaenoic acid exerts neuroprotective effect through improvement of the mitochondrial integrity and function in genotoxic stress evoked by DNA alkylation.

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