The essential fatty acid DHA (docosahexanoic acid) comprises 3% of the dry mass of the human brain. Dietary deficiency of DHA is associated with increased incidence of neurodegenerative disorders including Alzheimer's disease and subsequent brain cell death. Nutritional DHA deficiency also affects brain zinc homeostasis. Our previous work showed that DHA deficiency increased hippocampal zinc levels and raised the expression of the ZnT3 putative zinc transporter in the rat brain. We hypothesize that DHA deficiency induces neuronal cell death through zinc-induced apoptosis. To elucidate the link between DHA, zinc and brain cell death, we grew cultured human neuronal M17 cells in DHA-deficient and DHA-enriched culture medium. Exposure of M17 cells to DHA-deficient medium reduced the levels of active caspase-3 and increased the levels of Bcl2, relative to levels in DHA-replete cells, confirming the adverse effects of DHA deficiency in promoting neuronal cell death. To investigate the role of zinc in DHA-induced apoptotic cell death we grew cells in DHA-deficient and DHA-replete culture medium and measured zinc uptake using radiolabelled zinc. In DHA-deficient M17 cells, zinc uptake was 30% less in compared with that of DHA-replete cells. Furthermore, in DHA-treated cells, ZnT3 mRNA and protein levels were reduced compared to the levels in DHA-replete cells. Based on previous reports showing free zinc mediates brain cell death through apoptosis, we propose that neuroprotective function of DHA is exerted through a reduction in cellular zinc levels that in turn inhibits apoptosis.