

Role of DHA metabolites in protective effects of DHA supplementation in the brains of rotenone-induced rat models of Parkinson's disease

Ami Oguro and Yasuhiro Ishihara

Program of Biomedical Science, Graduate School of Integrated Sciences for Life, Hiroshima University

Docosahexaenoic acid (DHA) is the predominant omega-3 fatty acid in the brain and has been shown to have neuroprotective effects in Parkinson's disease, but the underlying mechanism has not been fully elucidated. DHA is metabolized to DHA epoxides (EDPs) and hydroxides by cytochrome P450s (P450s), and EDPs are further hydroxylated to the corresponding diols (DHDPs) by soluble epoxide hydrolase (sEH). In the present study, we investigated the roles of these DHA metabolites in the beneficial effects of DHA supplementation on a rotenone-induced rat model of Parkinson's disease. Metabolite analysis by LC-MS revealed that CYP2A1, 2C11, 2C13, 2C23, and 2E1 contributed to the formation of EDPs, and these P450s and sEH were expressed in the rat brain. We found that DHA supplementation in rats improved the motor dysfunction induced by rotenone. In addition, DHA reversed the decrease in tyrosine hydroxylase and the increase in lipid peroxidation generated by rotenone in the striatum. DHA supplementation also induced mRNA expression of antioxidant genes and Nrf2 protein expression in the striatum. However, these effects of DHA supplementation were eliminated by cosupplementation with the sEH inhibitor TPPU. DHA metabolites, including EDPs and DHDPs, in the rat brain were analyzed by LC-MS/MS. Supplementation with DHA increased the amount of DHA-diols (DHDPs) in the rat brain, while the amount of EDPs was not significantly increased. In addition, TPPU suppressed the increase in DHDPs and increased EDPs in the brain. These results indicate that DHDPs are important in the beneficial effects of DHA supplementation. The addition of DHDPs to PC12 cells increased the mRNA levels of antioxidant genes along with Nrf2 induction. This study suggests that DHA metabolites—DHDPs generated by P450s and sEH—have an important role in improving rotenone-induced Parkinson's disease.