Docosahexaenoic acid (DHA) is an ω-3 polyunsaturated fatty acid (PUFA) enriched in the brain and essential for brain development and function. Clinical studies have indicated that supplementation or dietary intake of DHA can alleviate the symptoms of neurodegenerative disorders such as Parkinson's disease. Epidemiological studies have also shown that intake of ω-3 PUFAs was consistently associated with a low risk of Parkinson's disease. Parkinson's disease is the second most prevalent neurodegenerative disease and is characterized clinically by motor deficits. Pathological features of Parkinson's disease include loss of dopaminergic neurons projecting from the substantia nigra to the striatum. Many reports have indicated that DHA has protective effects on dopaminergic neurons, but the underlying mechanism and molecular mediators are still unclear. In our body, DHA is metabolized to DHA epoxides, epoxygenase-catalyzed epoxides (EDPs) by cytochrome P450s (CYP, P450s), and EDPs are further hydroxylated to the corresponding diols, dihydroxyocosapentaenoic acids (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.

Introduction

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

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Effects of DHA and sEH inhibitor supplementation on motor dysfunction and loss of tyrosine hydroxylase (TH) expression in rotenone-induced rat models of Parkinson's disease

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

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1. Production of DHA metabolites, epoxidized forms (EDPs) by purified rat P450s

Purified rat P450 with cytochrome b5, NADPH-cytochrome P450 reductase, and diaphorase-phosphatidylcholine was incubated with 100 µM DHA and NADPH for 15 min, and the metabolites were analyzed by UPLC-MS. The analytes were detected by tandem TOF monitored by total ions at m/z 343.2.

EDPs were produced by CYP2A1, 2C11, 2C13, 2C23, and 2E1.

Quantification of endogenous DHA-epoxides (EDPs) and diols (DHDPs) in the rat brain by LC-MS/MS

(A) Lipid peroxidation of the rat striatum was analyzed by TBARS assay. (B) The mRNA expression of EDPs was analyzed by real-time PCR. (C) NF-κB-related factor (NFκB) was determined by cotreatment with the sEH inhibitor TPPTU, suggesting that DHA metabolites by sEH is important in the beneficial effects of DHA.

Quantification of endogenous DHA-epoxides (EDPs) and diols (DHDPs) in the rat brain by LC-MS/MS

(A) Lipid peroxidation of the rat striatum was analyzed by TBARS assay. (B) The mRNA expression of EDPs was analyzed by real-time PCR. (C) NF-κB-related factor (NFκB) was determined by cotreatment with the sEH inhibitor TPPTU, suggesting that DHA metabolites by sEH is important in the beneficial effects of DHA.

2. mRNA expression of EDP-producing P450s and sEH in the rat brain region

mRNA levels of EDP-producing P450s and sEH in the rat brain region were analyzed by real-time PCR. The mRNA expression levels were normalized to the expression of histone 3.

sEH mRNA was broadly expressed in each region of the brain.

Conclusions

The present study showed that DHA metabolites (19,20-DHDP) produced by P450s and sEH have an important role in the beneficial effects of DHA supplementation in the brains of rat models of Parkinson's disease. 19,20-DHDP will reduce oxidative stress by induction of Nrf2-regulating antioxidant genes in neuronal cells. At present, a clinical trial indicated that treatment with DHA is a valuable potential tool in the management of Parkinson's disease. The present study raise the possibility that 19,20-DHDP is more effective than DHA for improving Parkinson's disease.

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