Ciclo de Seminários em Biologia Humana e Ambiente

Mestrado em Biologia Humana e Ambiente. Departamento de Biologia Animal

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Brain injury in Alzheimer's disease 5×FAD mice fed DHA-enriched diets

As a major public health concern, Alzheimer's disease (AD) is a chronic neurodegenerative disorder and the leading cause of dementia worldwide, accounting for 60% to 70% of cases. This neurological condition is characterised by a progressive decline in memory, cognitive abilities, and behaviour, which ultimately results in impaired daily activities and social functioning. Assuming the premise that n-3 long-chain polyunsaturated fatty acids (n-3 LCPUFA), in particular docosahexaenoic acid (DHA, 22:6 n-3) are a safe and inexpensive link to a better mental health and well-being throughout life, this study aims to exploit the potential of novel and sustainable non-fish sources within a blue biotechnology framework for human dietary intervention. The elucidation of individual biological effects of DHA from microalga oils, such as the sustainable *Schizochytrium* sp., and commercial DHASCO, by targeting the brain across key metabolic pathways of disease, on the prevention and treatment of AD is a major topic underscoring the relevance of key nutrients in supporting neuroprotection. 40 five-week-old 5×FAD male mice, one of the most commonly used and commercially available AD mouse model, were assigned to 5 body weight-matched dietary groups with 8 mice each and fed isocaloric diets based on AIN-93M standard chow for rodents during 6 months. Each diet, with the exception of the control feed (non-supplemented group, control), enclosed a modified lipid fraction supplemented with 2% of: 1) linseed oil (LSO, rich in α-linolenic acid, the precursor of n-3 LCPUFA pathway); 2) cod liver oil (fish oil, FO rich in both DHA and EPA); 3) Schizochytrium sp. microalga oil (Schizo) with 40% of DHA; 4) commercial DHASCO oil (DHASCO) with 70% of DHA. We investigated the impact of different dietary n-3 LCPUFA formulations by targeting brain DHA enrichment and subsequent health condition through classical histology and immunohistochemistry techniques directed towards β-amyloid plaques deposition, TAU protein levels, and neuroinflammation. By the end of the experimental assay, no diet effects were observed on final body weight, daily feed intake and body weight gain ($p > 0.05$) of mice. Dietary n-3 LCPUFA influenced positively plasma metabolites ($p < 0.05$) as well as brain FA profile ($p < 0.05$), increasing DHA levels ($p < 0.05$). No systemic inflammation was observed in 5×FAD transgenic mice ($p > 0.05$). Hematoxylin & eosin classical staining was applied to evaluate neuronal density as a proxy of neuronal survival, with identical neurons count across diets, except for the fish oil diet with an increased number ($p = 0.031$) relative to linseed oil. Immunohistochemistry using antibodies directed against β-amyloid plaques showed that DHA-enriched diets promoted reduced plaques count ($p = 0.002$), while smaller β-amyloid plaques were positively observed only in the fish oil diet ($p = 0.007$). The histological detection of IBA1, a sensitive marker for microglial activation and therefore neuroinflammation, showed significant variations for both area ($p = 0.002$) and number of IBA1-positive cells ($p = 0.012$) amongst dietary groups, both parameters reduced in DHA-enriched diets. Immunostaining with TAU antibody showed reduced number of TAU-positive cells in mice fed Schizo diet relative to reference mice ($p = 0.028$).

Our data show the beneficial protection of DHA-enriched diets on neuronal survival and brain health in a traditional mouse model for AD research. These promising findings open new avenues for further studies focused on the beneficial effects of DHA derived from sustainable and underexploited *Schizochytrium* sp. microalga in the prevention of AD.

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