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Fat-1 Transgenic Mice: An Endogenous N-3 Polyunsaturated Fatty Acids Mouse Model is used in AD Research

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Abstract

Omega-3 polyunsaturated fatty acids (n-3 PUFAs) have been wildly considered for positive effect of Alzheimer's disease (AD). However, the intake of n-3 PUFAs is not encouraging to draw firm conclusion through preclinical and clinical research. The contribution of debate is derived from interference of dietary n-3 PUFAs, because of controlling the components and ratio of dietary PUFAs difficultly. In this context, transgenic fat-1 mouse that is capable of converting n-6 to n-3 fatty acids by feeding high n-6 PUFAs diet, leading to balance high n-3/n-6 PUFAs ratio, with increasing endogenous n-3 PUFAs and decreasing n-6 PUFAs in their organs and tissues. Thus, fat-1 mice is an ideal model to study the efficacy and mechanism of n-3 PUFAs in AD research, without the interference of the inevitable factors from dietary n-3 PUFAs. The fat-1 transgenic mice have become a useful tool for studying the potential benefit of endogenous n-3 PUFAs in behavior and neuromechanism of AD.

Keywords: Omega-3 polyunsaturated fatty acids; Alzheimer's disease; Transgenic fat-1 mouse

Alzheimer's disease (AD) is an age-related and progressive neurodegenerative disorder characterized by memory deficits and neuropsychiatric dysfunction and it is the most common cause of dementia [1]. Current statistics indicate that 44 million people throughout the world suffered from AD in 2015 and it is estimated that the populations will double by 2050 [2]. The neuropathological features in AD patients are presence of the abnormal depositions of amyloid-β peptide, the formation of intracellular neurofibrillary tangles (NFTs) and neurons lost [3]. Aggregated Aβ plays a pivotal role in the progression of AD, by activating oxidative stress to induce neurons death [1]. Therefore, Strategies for control of AD are associated with decreasing Aβ depositions and loss of neurons.

Omega-3 polyunsaturated fatty acids (n-3 PUFAs) have been broadly considered for reducing AD risk as a potential nutritional product. N-3 PUFAs are essential unsaturated fatty acids including α-linolenic acid (ALA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) [4]. Evidences suggest that n-3 PUFAs play an important role in the nervous system, maintaining the structural integrity of cell membranes and normal nerve function, as forming part of the cell membrane [5]. DHA is a key functional molecule to maintain brain development and function in the brain, which has been proved by He C's experiment. This study shows that DHA promotes differentiation and neurite outgrowth of neuronal cells, which is derived from mouse ES cells, also enhance the cells proliferation [6]. In addition, most preclinical studies demonstrated that n-3 PUFA supplementation could modulate AD neuropathology and prevent further progression [7]. At least 8 publications during the past 5 years have demonstrated that the treatment of mixed EPA and DHA or DHA alone supplementation could improve cognitive and neuronal variables in AD animal model [8]. Augment longchain n–3 PUFAs in the brain could reduce neuroinflammation [9] and oxidative stress [10] decreased hippocampal Aβ plaque density and prefibrillar Aβ oligomers [11], mitigated tau hyperphosphorylation [12], evenly restored spatial memory deficits, behavioral performance [13] and improved cognition [14,15]. However, some randomized clinical trials (RCT) indicated that dietary n-3 PUFAs did not show efficacy for advanced AD [16,17]. Thus, there is still insufficient conclusion to link n-3 PUFAs intake with AD improvement and some studies point out the conventional animal models with n-3 PUFAs dietary as the main driving factor behind these negative associations [18].

Due to generated restriction of n-3 PUFAs, dietary supplement is the only way to get n-3 PUFAs in humans and mammals. Dietary supplementation is a primary method to research the relationship between n-3 PUFAs intake and AD protection. However, this drawback of approach is difficult to control the dietary PUFAs components and ratio, which are easily interfered by feeds. For one reason, parts of lipid peroxide from n-3 PUFAs can increase Aβ production, which is positive to the progression of AD. For another reason, n-3 PUFAs agents are difficult to cross the blood-brain barrier, meaning the concentration is ineffective in brain [19]. Besides, Low n-3/n-6 PUFAs ratio contributes to the onset of AD. To avoid potential confounding dietary factors, Kang et al. [20] generated a transgenic mouse capable of synthesizing n-3 PUFAs endogenously (fat-1 mouse), which carried fat-1 gene from *Caenorhabditis elegans* can encodes n-3 desaturase that converts n-6 PUFAs to n-3 PUFAs by feeding high n-6 PUFAs diet. The advantage of fat-1 mice can increase the absolute amount of n-3 PUFAs and decrease the tissue level of n-6 PUFAs, leading to a balanced n-3/n-6 PUFAs ratio in body tissues without changing the mass of tissue fatty acids. Thus, fat-1 mice are suitable for crossing with wild-type (WT) mice or other AD model mice, which offspring is a good model that evaluates the impact of enriched n-3 PUFAs or appropriate n-6/n-3 PUFAs ratio in AD.

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Up to now, several studies have reported that endogenous n-3 PUFAs can improve neuropathology of AD by crossing fat-1 mice with other mice model. Lebbadi et al. [21] firstly used fat-1 mice crossing with 3xTg-AD mice to evaluate the effect of endogenous n-3 PUFAs to the neuropathology of AD. The results indicated that increasing endogenous n-3 PUFAs and keeping balance of n-3/n-6 PUFAs ratio showed efficacy against an AD-like neuropathology. Recently, another report [22] examined the neuronal protection of exogenous and endogenous DHA against $A\beta_{1-42}$ induced injury *in vitro* and *in vivo* by comparing fat-1 mice with WT mice. The results also demonstrated that endogenous DHA is neuroprotective via decreasing $A\beta_{1-42}$ oligomer-induced neuronal death. However, their research is still the lack of pathological and behavioral data drawing firm conclusion. Therefore, to accurately evaluate the impact of endogenous n-3 PUFAs on cognition and behavior in AD mice model, we crossed fat-1 mice with Swedish mutation human amyloid protein precursor $695^{K595N/M596L}$ (APP) transgenic mice, which like human age of AD onset. The data suggested enriched endogenous n-3 PUFAs in the brain could slow cognitive decline and prevent neuropsychological disorder in AD [23].

It is evident from the preceding discussion in understanding of the potential benefit of endogenous n-3 PUFAs in neuropathology and behavior of AD. Fat-1 mouse model has been proved to be an ideal animal model for endogenous n-3 PUFAs of AD research. However, the mechanism of the protective effect of PUFA on AD is still unclear. Previous reports have suggested that G-protein-coupled receptor 40 (GPR40) may be a functional therapeutic target for neuroprotection in the AD treatment [24]. GPR40 is a free fatty acid receptor throughout the primate brain, which can bind most of PUFAs and trigger GPR40 signaling pathway to provide neuro protection effect [25]. If combing GPR40 with rich endogenous n-3 PUFAs AD mice model based on fat-1 mice, it will enhance to clarify GPR40 functional role in the field of AD treated with n-3 PUFAs.

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