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Trabajo Original

Otros

Dietary fish oil increases catalase activity in patients with probable Alzheimer's disease

El aceite de pescado en la dieta aumenta la actividad de la catalasa en pacientes con probable enfermedad de Alzheimer

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Abstract

Background: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the presence of neuritic plaques and neurofibrillary tangles that finally result in synaptic and neuronal loss. Oxidative stress accompanies pathological changes in AD.

Objective: to assess the efficacy of dietary omega 3 polyunsaturated fatty acids supplementation on the levels of proteins oxidation, hydroperoxides and enzymatic activities of catalase and superoxide dismutase in AD patients.

Methods: clinical, controlled, randomized, double-blind trial. Patients consumed fish oil or placebo for one year. Oxidative stress markers were assessed in plasma using spectrophotometric methods.

Results: carbonyl groups in proteins and hydroperoxides in plasma have similar values in both treatment groups at the beginning of the study. At six and 12 months of treatment, these values decreased significantly in the fish oil group, while in the placebo group no changes were observed in both oxidative stress markers. Catalase activity increased significantly at six and twelve months after treatment in patients treated with fish oil. While the superoxide dismutase activity was not modified in both study groups.

Conclusions: patients who consume omega 3 polyunsaturated fatty acids at a stable dose of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) show decreased oxidation of proteins and lipids in plasma. In addition, an increase in catalase activity was detected. Thus, the presented data warrants further studies evaluating the antioxidant effect of omega 3 polyunsaturated fatty acids.

Keywords:

Alzheimer's disease. Oxidative stress. Omega 3 polyunsaturated fatty acids. Catalase. Protein carbonyls.

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Resumen

Antecedentes: la enfermedad de Alzheimer (EA) es un trastorno neurodegenerativo caracterizado por la presencia de placas neuríticas y ovillos neurofibrilares que finalmente resultan en pérdida sináptica y neuronal. El estrés oxidativo acompaña los cambios patológicos en la EA.

Objetivo: evaluar la eficacia de la suplementación dietética con ácidos grasos poliinsaturados omega 3 sobre los niveles de oxidación de proteínas, hidroperóxidos y actividades enzimáticas de catalasa y superóxido dismutasa en pacientes con EA.

Métodos: ensayo clínico, controlado, aleatorizado, doble ciego. Los pacientes consumieron aceite de pescado o placebo durante un año. Los marcadores de estrés oxidativo se evaluaron en plasma mediante métodos espectrofotométricos.

Resultados: los grupos carbonilo en proteínas e hidroperóxidos en plasma tuvieron valores similares en ambos grupos de tratamiento al inicio del estudio. A los seis y 12 meses de tratamiento estos valores disminuyeron significativamente en el grupo de aceite de pescado, mientras que en el grupo placebo no se observaron cambios en ambos marcadores. La actividad de catalasa aumentó significativamente a los seis y doce meses después del tratamiento en pacientes tratados con aceite de pescado; sin embargo, la actividad superóxido dismutasa no se modificó en ambos grupos de estudio.

Conclusiones: los pacientes que consumieron los ácidos grasos poliinsaturados omega 3 a una dosis estable de ácido docosahexaenoico (DHA) y ácido eicosapentaenoico (EPA) muestran una oxidación reducida de proteínas y lípidos en plasma. Además, se detectó un aumento en la actividad de la catalasa. Por tanto, los datos presentados justifican más estudios que evalúen el efecto antioxidante de dichos ácidos grasos.

Palabras clave:

Enfermedad de Alzheimer. Estrés oxidativo. Ácidos grasos poliinsaturados omega 3. Catalasa. Carbonilos proteicos.

INTRODUCTION

The most common form of presentation of all dementias is Alzheimer's disease (AD), characterized by a progressive neurodegenerative process that affects large areas of the cerebral cortex and hippocampus. Abnormalities are generally detected first in brain tissue involving the frontal and temporal lobes, subsequently progressing to other areas of the neocortex at rates that vary considerably between individuals. The characteristic pathological findings of AD are accumulation of amyloid β peptide (Aβ) in neuritic plaques, hyperphosphorylation of tau protein, and degeneration of neurons in brain regions such as the hippocampus, resulting in progressive cognitive dysfunction (1). With regard to the underlying alterations of the disease, participation by oxidative damage caused by free radicals has been demonstrated. The brain is particularly vulnerable to oxidative stress because it contains abundant polyunsaturated fatty acids; in addition, it consumes more oxygen per gram compared to other tissues and has less antioxidant capacity. The initial contribution of oxidative stress in Alzheimer's disease is demonstrated by oxidative modifications of lipids, proteins, and nucleic acids in the brain of these patients, as well as in cellular and animal models of AD. Likewise, βA has been shown to induce membrane lipid oxidation (2).

Epidemiological evidence suggests that people with a high intake of antioxidants in their diet have lower rates of AD (3,4). Similarly, some clinical trials have reported beneficial effects in older people with mild cognitive impairment with supplementation with long chain omega-3 polyunsaturated fatty acids (PUFAs), such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) (5). Furthermore, a cohort study in older men and women reported that higher serum concentrations of PUFAs were significantly associated with better patient performance on neuropsychological test. Elevated levels of EPA + DHA are significantly associated with a lower risk of dementia (6). In a meta-analysis, a beneficial effect of the consumption of these fatty acids was demonstrated in people with mild cognitive impairment in the subdomains of attention and processing speed (7). PUFAs are mainly incorporated into phospholipids, sphingolipids and plasmalogens and contribute to modulate the biophysical properties of cell membranes (fluidity, shape and thickness, permeability) and the activity of transmembrane proteins (8). Doses of between 2 and 6 g of DHA have shown incorporation into plasma phospholipids and this is increased in a dose-dependent manner (9). Previous data of our laboratory shows that dietary supplementation with fish oil has the following beneficial effects in patients diagnosed with probable Alzheimer's disease: it decreases plasma levels of lipoperoxides and nitric oxide catabolites and increases the ratio of reduced glutathione/oxidized glutathione. These changes are in parallel with the decrease in the ratio of omega 6 fatty acids/omega 3 fatty acids in erythrocytes (10). In the present study, the efficacy of omega 3 supplementation was evaluated in these patients by assessing the levels of proteins oxidation, hydroperoxides and enzymatic activities of catalase and superoxide dismutase.

MATERIALS AND METHODS

STUDY DESIGN

A randomized, double-blind clinical trial was conducted at the Cognitive Impairment Clinic of the Neurology Department of the Western National Medical Center, Mexican Social Security Institute in Guadalajara, Jalisco, Mexico. This study was conducted in accordance with the updated Declaration of Helsinki and all procedures were approved by the Ethics and Health Research Committee of the Mexican Social Security Institute (protocol number: 2014-785-011).

The diagnosis of AD was made by: a) a Mini Mental State Assessment (MMSE) (11) performed during the first visit, with a score of less than 25 for literate people and 20 for non-literate people; 2) DSM-V criteria for dementia (12); and 3) NINCDS-ADRDA diagnostic criteria (13). The patients had at least 2.5 years of history of cognitive decline. The criteria for excluding patients were: consumption of antioxidant supplements, histo-

ry of acute kidney or liver dysfunction, tobacco, drug or alcohol abuse, intolerance, contraindication or allergy to fish oil. Twenty patients diagnosed with probable AD were randomized 1:1 to receive oral fish oil or placebo, with a computer-generated randomization sequence. Fish oil and placebo were administered in gel dosage form and to ensure masking the gels were identical in appearance, packaging, and labeling. Randomization and allocation were concealed from investigators and patients until the end of the study. Identification numbers were assigned to ensure patient confidentiality. Informed consent was obtained from the patient and the caregiver. Patients took one gel orally per day. The fish oil gels contained 0.45 g of EPA and 1 g of DHA. Participants reported daily consumption of the supplement on a consumption record sheet. The rate of adherence to treatment was greater than 80 %.

OXIDATIVE STRESS MARKERS ASSESSMENT

At the beginning of treatment and every six months a blood sample was drawn from the patients to evaluate oxidative stress markers. Blood samples were collected in tubes with 0.1 % ethylenediaminetetraacetic acid (EDTA) and the plasma was separated by centrifugation at 2,000 rpm for ten minutes at room temperature. The samples were stored at -80 °C degrees until use. All optical density readings were made with a UV/VIS spectrophotometer (Benchmark™ Plus Microplate from BioRad; Hercules, CA, USA).

The levels of carbonyl groups in proteins were quantified according to Lenz AG et al. (14) with minor modifications as follows: to 0.2 ml of plasma 1 ml of 10 mM 2,4-dinitrophenylhydrazine was added dissolved in 2M HCl. The samples were incubated for one hour at room temperature and 333 µl of trichloroacetic acid (30 %, w/v) were added. Then, the suspension was centrifuged at 14,000 rpm for 20 minutes. The resulting precipitate was washed three times with 1 ml of ethyl acetate ethanol solution (1:1). The supernatant was discarded and the final pellet was dissolved with 1 ml of 6M guanidine hydrochloride and incubated for 15 minutes at room temperature. The absorbance of the samples was read at 370 nm.

Hydroperoxide quantitation was determined with 0.1 ml of plasma mixed with 0.9 ml of reaction medium (100 mM xylene orange, 250 mM ferrous ammonium sulfate, 25 mM sulfuric acid, and 4 mM butylhydroxytoluene in 90 % methanol). The samples were incubated for 30 minutes at room temperature and then centrifuged at 10,000 rpm for five minutes. The absorbance of the supernatant was read at 560 nm. A standard curve was run with known concentrations of hydrogen peroxide (15).

Catalase activity was assessed with 0.1 ml of plasma mixed with 0.9 ml of reaction medium (65 mM hydrogen peroxide in 60 mM phosphate buffer, pH = 7.4) and incubated at 37 °C for two minutes. The reaction was stopped with 2 ml of 32.4 mM ammonium molybdate. The absorbance of the samples was recorded at 374 nm to quantify the hydrogen peroxide remaining in the reaction (16).

Superoxide dismutase activity was quantified using a reagent kit (No. 706002, Cayman Chemical Company®, USA). The manufacturer's instructions were followed for the detection of superoxide anion generated by the enzyme xanthine oxidase and hypoxanthine by reaction with tetrazolium salt. Plasma samples were diluted 1:5 in sample buffer and 0.2 ml of the radical detector was added to 10 µl of diluted plasma. After slow stirring, 20 µl of xanthine oxidase was added and the samples were incubated for 20 minutes at room temperature and the absorbance was read at a wavelength of 440 nm. Superoxide dismutase activity is reported in U/ml.

STATISTICAL ANALYSIS

Data were analyzed as mean values ± standard deviation. The differences in the parameters studied between the groups were evaluated by analysis of variance (ANOVA) and the Mann-Whitney U test. A p value < 0.05 was considered as statistically significant. The analyzes were performed in SPSS version 21.

RESULTS

CHARACTERISTICS OF THE STUDY POPULATION

Of a total of 87 AD patients treated at the Neurology Department's Cognitive Impairment Clinic, 20 met the inclusion criteria and were randomly assigned to receive fish oil (ten patients) or placebo (ten patients). At the end of the intervention, 17 patients completed the one-year trial. In the fish oil group, two patients withdrew from the study, one due to lack of adherence to treatment and the other due to intolerance to the taste of fish. In the placebo group, one patient discontinued their participation in the study due to the development of high blood pressure.

OXIDATIVE STRESS MARKERS

Figures 1A and 1B exhibit that plasma levels of carbonyl groups in proteins and hydroperoxides, respectively, have similar values in both treatment groups at the beginning of the study. However, at six and 12 months the values decreased significantly in the fish oil group, while in the group treated with placebo no changes were observed in both oxidative stress markers at six and 12 months.

The enzymatic activities of catalase and superoxide dismutase (Figures 1C and 1D, respectively) in plasma at the start of treatment were similar in both study groups. Catalase activity increased significantly at six and 12 months after treatment only in patients treated with fish oil. While the superoxide dismutase activity is not modified in neither of the two study groups.

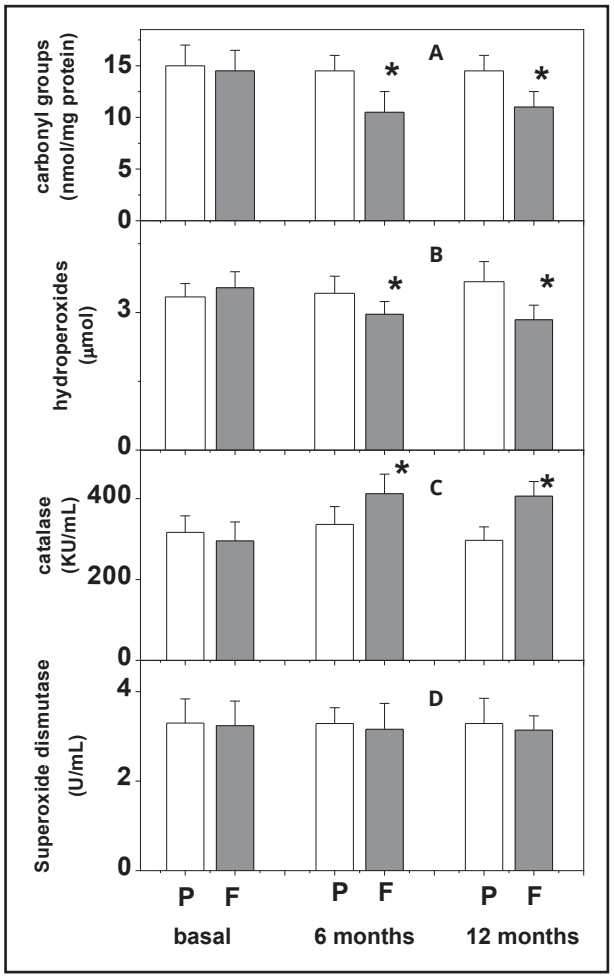

Figure 1.

Plasma levels of biochemical markers at the beginning and after six and 12 months of treatment in the placebo (P) and fish oil (F) group. Levels of carbonyl groups in proteins (A), hydroperoxides (B), catalase activity (C) and superoxide dismutase activity (D). Data are expressed as mean ± standard deviation. The comparison was calculated with the Mann-Whitney U test. *$p < 0.05$.

DISCUSSION

Oxidative stress plays an important role in the pathogenesis of AD. In the present study, it was found that patients who consume PUFAs at a stable dose of DHA and EPA show decreased oxidation of plasma proteins and lipids in addition to an increase in catalase activity. This beneficial effect may be important, since the increase in production of reactive oxygen species (ROS) associated with AD affects mitochondrial activity, metal homeostasis and the deterioration of antioxidant defense, which directly affects synaptic activity and neurotransmission, which leads to cognitive deterioration. Abnormal cellular metabolism in AD affects the production and accumulation of amyloid and hyperphosphorylated tau protein, which could independently exacerbate mitochondrial dysfunction and contribute to ROS production, thus preserving a vicious cycle to the detriment of cognitive function (17).

Recent evidence suggests that the actions derived from PUFAs are mediated through oxidative and non-oxidative metabolic pathways that convert them to bioactive lipid metabolites. One of the non-oxidative pathways involves the conversion of DHA and EPA to the endocannabinoids docosahexaenoyl ethanolamide and eicosapentaenoyl ethanolamide, which have similar effects to those of Δ9-tetrahydrocannabinol. Endocannabinoids play important physiological roles that are mainly exerted through activation of the cannabinoid receptor-1 (CB1) and -2 (CB2). CB1 is found predominantly in the CNS, and CB2 is found in peripheral immune cells. DHEA has anticancer, anti-inflammatory, and synaptogenic properties (18). Additionally, the following effects of omega 3 fatty acids have been demonstrated: a) their anti-inflammatory effect, which is based on the down regulation of nuclear factor kB (19); b) the production of oxygenated metabolites of EPA and DHA that actively promote the resolution of inflammation, such as resolvins and protectins (20); and c) its effect on modifying the biophysical properties of the membranes resulting in changes in the activity of ion channels, receptors and the binding between phospholipids and proteins, which may be important, due to the nature of the interaction of the membranes with the β-amyloid peptide (21).

DHA has also been shown to decrease β-amyloid peptide levels, regulate the activity of anti-apoptotic genes such as Bcl-2, BCl-xl, and Bfl-1 (22), and modulate the phosphatidyl inositol 3-kinase-Akt pathway (23). Similarly, DHA augments angiongenesis and neurogenesis in an *in vivo* model (24). On the other hand, with respect to the estimated half-life of DHA in the brain, it has been identified that it is approximately 2.5 years, its bioavailability begins with ingestion from which it is incorporated very quickly into the membrane phospholipids of many tissues and relatively little time is required to observe its effects (25). The incorporation of DHA into cholesterol esters reflects the consumption of DHA in the previous 1-2 weeks. In erythrocyte membranes, its consumption is reflected in the previous 1-2 months and in adipose tissue from a period of previous years of consumption (26). Measurements of DHA levels in erythrocytes and plasma have been correlated with its concentration in the brain, retina, and liver. Stopping the intake of DHA as a supplement results in a rapid release of this lipid from the plasma membrane. This shows that the constant consumption of DHA is necessary to maintain its effect on the lipid rafts of the plasma membranes (9).

Consistent with the above, it is known that DHA increases the binding of soluble oligomers of amyloid β peptide to membrane phospholipids and this has a beneficial effect (27). Therefore, elevated levels of EPA and DHA in the plasma membrane can affect the metabolism of amyloid β peptide and reduce the risk or progression of Alzheimer's disease. Additionally, in this work it was found that the increase in the content of EPA and DHA in erythrocytes is associated with an improvement in the fluidity of the membranes. This can be attributed to the fact that EPA and DHA exert some of their metabolic functions as part of the structure of the phospholipids that make up cell membranes, particularly phosphatidylcholine and phosphatidylserine. Due to their high degree of polyunsaturation, these fatty acids provide fluidity to the membranes, an essential characteristic that allows the mobility of proteins, either on the surface or inside the lipid bilayer (28).

CONCLUSION

The oxidative stress markers analyzed in this clinical trial, such as the oxidation of proteins and lipids, were decreased with the consumption of omega 3 polyunsaturated fatty acids in patients with AD, and this decrease is correlated with an increase in catalase activity.

REFERENCES

1. DeTure MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. Mol Neurodegeneration 2019;14:32. DOI: 10.1186/s13024-019-0333-5
2. Buckner RL. Memory and executive function in aging and AD. Neuron 2004;44(1):195-208. DOI: 10.1016/j.neuron.2004.09.006
3. Steele M, Stuchbury G, Munch G. The molecular basis of the prevention of Alzheimer's disease through healthy nutrition. Exp Gerontol 2007;42:28-36. DOI: 10.1016/j.exger.2006.06.002
4. Schaefer EJ, Bongard V, Beiser AS, Lamon-Fava S, Robins SJ, Au R, et al. Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease. Arch Neurol 2006;63(11):1545. DOI: 10.1001/archneur.63.11.1545
5. Zhang Y, Lou Y, Hu J, Miao R, Ma F. DHA supplementation improves cognitive function via enhancing Aβ-mediated autophagy in Chinese elderly with mild cognitive impairment: a randomized placebo-controlled trial. Neurol Neurosurg Psychiatry 2018;89(4):382-8. DOI: 10.1136/jnnp-2017-316176
6. Ammann EM, Pottala JV, Robinson JG, Espeland MA, Harris WS. Erythrocyte omega-3 fatty acids are inversely associated with incident dementia: secondary analyses of longitudinal data from the Women's Health Initiative Memory Study (WHIMS). Prostaglandins Leukot Essent Fatty Acids 2017;121:68-75. DOI: 10.1016/j.plefa.2017.06.006
7. Mazereeuw G, Lanctôt KL, Chau SA, Swardfager W, Herrmann N. Effects of omega-3 fatty acids on cognitive performance: a meta-analysis. Neurobiol Aging 2012;33(7). DOI: 10.1016/j.neurobiolaging.2011.12.014
8. Hishikawa D, Valentine WJ, Iizuka-Hishikawa Y, Shindou H, Shimizu T. Metabolism and functions of docosahexaenoic acid-containing membrane glycerophospholipids. FEBS Lett 2017;591(18):2730-44. DOI: 10.1002/1873-3468.12825
9. Arterburn LM, Hall EB, Oken H. Distribution, interconversion, and dose response of n-3 fatty acids in humans. Am J Clin Nutr 2006;83(6 Suppl):1467S-76S. DOI: 10.1093/ajcn/83.6.1467S
10. Sánchez-Romero L, Pacheco-Moisés FP, El Hafidi M, Mireles Ramírez MA, Cruz-Serrano JA, Velázquez-Brizuela IE, et al. Effect of fish oil on oxidative stress markers in patients with probable Alzheimer's disease. Arch Latinoam Nutr 2020;70(2):123-33.
11. Folstein MF, Folstein SE, McHugh PR. "Mini mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatry Res 1975;12(3):189-98. DOI: 10.1016/0022-3956(75)90026-6
12. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th edition. Washington, DC: American Psychiatric Association; 2013. DOI: 10.1176/appi.books.9780890425596
13. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34(7):939-44. DOI: 10.1212/WNL.34.7.939
14. Lenz AG, Costabel U, Shaltiel S, Levine RL. Determination of carbonyl groups in oxidatively modified proteins by reduction with tritiated sodium borohydride. Anal Biochem 1989;177(2):419-25. DOI: 10.1016/0003-2697(89)90077-8
15. Jiang ZY, Hunt JV, Wolff SP. Ferrous ion oxidation in the presence of xylenol orange for detection of lipid hydroperoxide in low density lipoprotein. Anal Biochem 1992;202(2):384-9. DOI: 10.1016/0003-2697(92)90122-N
16. Hadwan MH, Abed HN. Data supporting the spectrophotometric method for the estimation of catalase activity. Data Brief 2015;6:194-9.
17. Tönnies E, Trushina E. Oxidative stress, synaptic dysfunction, and Alzheimer's disease. J Alzheimer's Dis 2017;57(4). DOI: 10.3233/JAD-161088
18. McDougle DR, Watson JE, Abdeen AA, Adili R, Caputo MP, Krapf JE, et al. Anti-inflammatory ω-3 endocannabinoid epoxides. Proc Natl Acad Sci USA 2017;114(30):E6034-43. DOI: 10.1073/pnas.1610325114
19. Lillis AP, Van Duyn LB, Murphy-Ullrich JE, Strickland DK. LDL receptor-related protein 1: unique tissue-specific functions revealed by selective gene knockout studies. Physiol Rev 2008;88(3):887-918. DOI: 10.1152/physrev.00033.2007
20. Mandrekar S, Jiang Q, Lee CY, Koenigsknecht-Talboo J, Holtzman DM, Landreth GE. Microglia mediate the clearance of soluble Abeta through fluid phase macropinocytosis. J Neurosci 2009;29(13):4252-62. DOI: 10.1523/JNEUROSCI.5572-08.2009
21. Jones PB, Adams KW, Rozkalne A, Spires-Jones TL, Hshieh TT, Hashimoto T, et al. Apolipoprotein E: isoform specific differences in tertiary structure and interaction with amyloid-β in human Alzheimer brain. PLoS One 2011;6(1):e14586. DOI: 10.1371/journal.pone.0014586
22. Bazan NG. Docosanoids and elovanoids from omega-3 fatty acids are pro-homeostatic modulators of inflammatory responses, cell damage and neuroprotection. Mol Aspects Med 2018;64:18-33. DOI: 10.1016/j.mam.2018.09.003
23. Akbar M, Calderon F, Wen Z, Kim HY. Docosahexaenoic acid: a positive modulator of Akt signaling in neuronal survival. Proc Natl Acad Sci USA 2005;102:10858-63. DOI: 10.1073/pnas.0502903102
24. Belayev L, Hong SH, Menghani H, Marcell SJ, Obenaus A, Freitas RS, et al. Docosanoids promote neurogenesis and angiogenesis, blood-brain barrier integrity, penumbra protection, and neurobehavioral recovery after experimental ischemic stroke. Mol Neurobiol 2018;55(8):7090-106. DOI: 10.1007/s12035-018-1136-3
25. Umhau JC, Zhou W, Carson RE, Rapoport SI, Polozova A, Demar J, et al. Imaging incorporation of circulating docosahexaenoic acid into the human brain using positron emission tomography. J Lipid Res 2009;50:1259-68. DOI: 10.1194/jlr.M800530-JLR200
26. Katan MB, Deslypere JP, van Birgelen APJM, Penders M, Zegwaars M. Kinetics of the incorporation of dietary fatty acids into serum cholesteryl esters, erythrocyte membranes and adipose tissue: an 18 month controlled study. J Lipid Res 1997;38:2012-22. DOI: 10.1016/S0022-2275(20)37132-7
27. Goedert M, Spillantini MG. A century of Alzheimer's disease. Science 2006;314(5800):777-81. DOI: 10.1126/science.1132814
28. Wassall SR, Leng X, Canner SW, Pennington ER, Kinnun JJ, Cavazos AT, et al. Docosahexaenoic acid regulates the formation of lipid rafts: a unified view from experiment and simulation. Biochim Biophys Acta Biomembr 2018;1860(10):1985-93. DOI: 10.1016/j.bbamem.2018.04.016