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Potential Role of Brain-Derived Neurotrophic Factor in Omega-3 Fatty Acid Supplementation to Prevent Posttraumatic Distress after Accidental Injury: An Open-Label Pilot Study

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It is known that severity of depression is associated with low levels of erythrocyte omega-3 polyunsaturated fatty acids (n-3 PUFA) [1] and serum brain-derived neurotrophic factor (BDNF) [2]. Dietary n-3 PUFA promote the maturation of neurons and hippocampal neurogenesis in adult rats [3] and have been found to increase the levels of BDNF in rat hippocampus [4, 5]. BDNF exerts various effects on the nervous system, including neuronal outgrowth, differentiation, synaptic connectivity as well as neuronal repair and survival during development and in adulthood [6–8]. These findings indicate that supplementation with n-3 PUFA enhances the effect of BDNF-related synaptic plasticity and neurogenesis.

Recently, Kitamura et al. [9] have shown that hippocampal neurogenesis contributes to the clearance of artificially induced fear memory in mice. It is suggested that adult neurogenesis may play a role in the periodic clearance of hippocampal memory traces in contextual fear conditioning. Therefore, we hypothesized that n-3 PUFA-induced neurogenesis occurring early in the transition period might, by increasing BDNF, facilitate the clearance of fear memory and attenuate posttraumatic distress as a consequence. The aims of the present study were to answer the following questions: whether supplementation with n-3 PUFA increases serum levels of BDNF, and whether change in serum BDNF is associated with the alleviation of posttraumatic distress at follow-up in our pilot trial [10].

From among 122 consecutive patients who were recruited from the intensive care unit of the National Disaster Medical Center within 240 h of accidental injury during a 23-week period, 27 met the inclusion criteria. Of these 27 eligible patients, 15 agreed to and provided prior written informed consent to participate in

the study. The study protocol was reviewed and approved by the institutional review boards and registered at <http://clinicaltrials.gov/> as NCT00671489. Of the 15 patients enrolled, 11 completed the 12-week follow-up. Three patients cancelled a visit at the last minute and 1 lost contact after the 4-week follow-up visit. Patients who completed the trial did not significantly differ from those who did not complete the trial in terms of sex, age, vital signs, and injury severity score [11], Glasgow Coma Scale [12] and peritraumatic distress inventory scores [13].

A total of 7 n-3 PUFA capsules (Kentech Co. Ltd., Japan) containing 1,470 mg docosahexaenoic acid (22:6 n-3) and 147 mg eicosapentaenoic acid (20:5 n-3) were administered daily for 12 weeks in an open-label fashion. Trained psychiatrists assessed posttraumatic stress disorder (PTSD) and major depressive disorder (MDD) by structured clinical interviews [14, 15] at weeks 4 and 12. The interrater reliability for diagnosis of PTSD and MDD was reliable, with κ values of 1.0 and 0.9, respectively [16]. To assess the serum BDNF levels, 7–10 ml of whole blood were obtained in ethylenediaminetetraacetic acid tubes in the emergency room (week 0), and in week 4 and week 12. Serum BDNF levels were measured using the BDNF Emax Immunoassay System Kit (Promega, Madison, Wisc., USA).

The difference between serum BDNF levels at weeks 0 and 12 was compared by paired t test. Scatter plots show the association between the changes in serum BDNF levels and posttraumatic distress as determined by the structured interview at weeks 4 and 12. The distress group consisted of those patients who met the criteria for MDD or PTSD during the trial. We then examined the intergroup differences in changes in serum BDNF levels from week 0 to the endpoint at week 12 using the Wilcoxon rank-sum test. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

During the first 4 weeks after accident, 1 patient met the criteria for PTSD and remained essentially the same at week 12. Another patient met the criteria for MDD at the 4-week follow-up, but symptoms had disappeared at the 12-week follow-up. Overall, serum BDNF levels were significantly elevated from week 0 to week 12 [$n = 11$; 52.36 ng/ml (SD = 16.69) vs. 79.83 ng/ml (SD = 13.79); $p = 0.001$], although they were largely unchanged in the distress group (fig. 1). Changes in BDNF levels between weeks 0 and 12 were significantly greater in the nondistressed group than in the distress group (median 33.5 ng/ml, range 8.5–56.0 vs. median 5.4 ng/ml, range 4.4–6.4; $p = 0.037$). There was no significant association between changes in serum BDNF level and age, sex, injury severity score, vital signs or peritraumatic distress inventory score (data not shown).

We confirmed that supplementation with n-3 fatty acids increased serum BDNF levels. As shown in the figure, the changes seen in serum BDNF levels might be associated with reduced posttraumatic distress on follow-up. Although the present study

Fig. 1. Supplementation with n-3 PUFA increased serum BDNF levels in accident-injured patients. Solid lines (n = 2): patients who developed PTSD or MDD during the trial. Dotted lines (n = 9): patients who did not develop a psychiatric illness during the trial. Squares: patients who dropped out (n = 4). ER = Emergency room; 4W and 12W = 4- and 12-week follow-up assessments.

was not a placebo-controlled trial, the results suggest a potential role for BDNF in the prevention of posttraumatic distress by n-3 fatty acid supplementation.

As to previous research, an animal study indicated that a docosahexaenoic acid-enriched diet increased levels of pro-BDNF and mature BDNF in the hippocampus [4]. In a postmortem brain study, increased hippocampal BDNF expression was found in subjects treated with antidepressant medications compared with untreated subjects [17]. Serum BDNF levels in antidepressant-treated patients with MDD were higher than in untreated MDD patients [2]. In addition, Venna et al. [18] showed that dietary supplementation with n-3 PUFA containing 70% α -linolenic acids for more than 5 weeks exerted antidepressant-like effects, and was associated with an increase in hippocampal volume, an overexpression of synaptophysin and BDNF, and an increase in the number of newborn cells in mice. A significant correlation was found between n-3 PUFA consumption and gray matter volume in the amygdala, hippocampus and anterior cingulate cortex in healthy adults [19]. Against such a background, the preventive effect on posttraumatic distress of n-3 PUFA supplementation seen in the present study may well be due to an antidepressant effect, alongside structural and molecular changes occurring in the hippocampus. To overcome the limitations of our study such as the small sample size and the lack of a parallel control group, we have started a randomized controlled trial (NCT00671099).

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