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Dietary Omega-3 Fatty Acids Normalize BDNF Levels, Reduce Oxidative Damage, and Counteract Learning Disability after Traumatic Brain Injury in Rats

AIGUO WU,[1] ZHE YING,[1] and FERNANDO GOMEZ-PINILLA[1,2]

ABSTRACT

Omega-3 fatty acids (i.e., docosahexaenoic acid; DHA) regulate signal transduction and gene expression, and protect neurons from death. In this study we examined the capacity of dietary omega-3 fatty acids supplementation to help the brain to cope with the effects of traumatic injury. Rats were fed a regular diet or an experimental diet supplemented with omega-3 fatty acids, for 4 weeks before a mild fluid percussion injury (FPI) was performed. FPI increased oxidative stress, and impaired learning ability in the Morris water maze. This type of lesion also reduced levels of brain-derived neurotrophic factor (BDNF), synapsin I, and cAMP responsive element-binding protein (CREB). It is known that BDNF facilitates synaptic transmission and learning ability by modulating synapsin I and CREB. Supplementation of omega-3 fatty acids in the diet counteracted all of the studied effects of FPI, that is, normalized levels of BDNF and associated synapsin I and CREB, reduced oxidative damage, and counteracted learning disability. The reduction of oxidative stress indicates a benevolent effect of this diet on mechanisms that maintain neuronal function and plasticity. These results imply that omega-3 enriched dietary supplements can provide protection against reduced plasticity and impaired learning ability after traumatic brain injury.

Key words: BDNF; fish oil; hippocampus; learning; traumatic brain injury

INTRODUCTION

Traumatic brain injury (TBI) is a major cause of disability such that a great concern exists to develop means to decrease its short- and long-term effects. Dietary factors are emerging as an efficient means to modulate the capacity of the brain for plasticity (Mattson et al., 2003; Wu et al., 2004). Docosahexaenoic acid (DHA; C22: 6n-3), one of the major omega-3 polyunsaturated fatty acids in the brain, has shown to be essential for normal neurological development, maintenance of learning and memory, and neuronal plasticity (Green and Yavin, 1998; Hashimoto et al., 2002; Salem et al., 2001). DHA can affect neural function by enhancing synaptic membrane fluidity and function (Jump, 2002), regulating gene expression (Duplus et al., 2000; Ikemoto et al., 2000; Kitajka et al., 2002; Puskas et al., 2003; Salem et al., 2001), mediating cell signaling (de Urquiza et al., 2000; Jump, 2002; Vaidyanathan et al., 1994;), and enhancing long-term potentiation (LTP) (McGahon et al., 1999). Dietary

[1]Department of Physiological Science, University of California at Los Angeles, and [2]Division of Neurosurgery, UCLA Brain Injury Research Center, Los Angeles, California.

DHA supplementation improves learning ability (Lim and Suzuki, 2001; Suzuki et al., 1998) and enhances long-term memory in both young and old animals (Gamoh et al., 1999, 2001; Lim and Suzuki, 2000), and can reduce cognitive decay during aging and Alzheimer's disease (Hashimoto et al., 2002). Therefore, it is possible that select dietary components ingested at the appropriate time can be used to overcome some of the deleterious effects of TBI on brain function.

It is well accepted that cognitive dysfunction is a prevalent consequence of TBI in humans (Borgaro et al., 2003; Piot-Grosjean et al., 2001) and animals (Fox et al., 1998; Smith et al., 1995; Wu et al., 2003). TBI is associated with a long-lasting decrement in the capacity of the brain to cope with future insults, and often with a reduced ability of individuals to maintain higher cognitive and intellectual function. Although cells may undergo differential degrees of degeneration, the large majority of neurons survive the primary insult (Hovda et al., 1995). It is, therefore, believed that neuronal death by itself cannot completely explain the chronic functional problems experienced by TBI patients (Lyeth et al., 1990; Scheff et al., 1997), and that these problems may reside in disrupted molecular mechanisms governing synaptic transmission.

The BDNF system enhances the function and viability of select neuronal populations, and its action appears to be crucial for maintaining molecular processes underlying cognitive function. BDNF promotes neuronal excitability (Bolton et al., 2000; Kafitz et al., 1999) and facilitates synaptic transmission (Kang and Schuman, 1996; Levine et al., 1998; Sherwood and Lo, 1999; Tyler and Pozzo-Miller, 2001), and hippocampal BDNF seems necessary for the induction of LTP (Korte et al., 1995; Linnarsson et al., 1997; Patterson et al., 1996). BDNF is synthesized predominantly by neurons located in the hippocampus, a brain region intimately associated with the processing of cognitive function (Drapeau et al., 2003; Kelly et al., 2003; Steffenach et al., 2002; Sugaya et al., 1996). Synapsin I is a nerve terminal phospho-protein involved in neurotransmitter release, axonal elongation and maintenance of synaptic contacts (Brock and O'Callaghan, 1987; Wang et al., 1995), whose synthesis (Wang et al., 1995) as well as phosphorylation (Jovanovic et al., 1996) are affected by BDNF. CREB, a transcription factor involved in learning and memory, is an important modulator of gene expression induced by BDNF (Finkbeiner, 2000). It is possible that TBI can compromise the BDNF system, weakening the molecular substrates for maintaining neuronal function. We also hypothesize that enhanced function of the BDNF system by omega-3 fatty acids can be an effective therapy to reduce cognitive impairment after TBI.

MATERIALS AND METHODS

Experimental Design and Tissue Preparation

Male Sprague-Dawley rats ($n = 48$, Charles River Laboratories, Inc., Wilmington, MA) weighing between 200 and 240 g were housed in cages (two rats per cage) and maintained in environmentally controlled rooms (22–24°C) with a 12-h light/dark cycle. After acclimatization for 1 week on standard rat chow, the rats were randomly assigned to regular diet (RD; 0.9% DHA and 1% eicosapentaenoic acid (EPA). In this diet total fat content, 4.5%; total saturated fat, 1.5%; total monounsaturated, 1.58%) or diet containing 8% fish oil (FO; 12.4% DHA and 13.5% EPA. In this diet total fat content: 10.4%; total saturated fat, 2.8%; total monounsaturated, 2.29%) for 4 weeks. Omega-3 fatty acids from FO have been shown to provide beneficial effects on rodent brain (Kitajka et al., 2002; Puskas et al., 2003). The diets, fed *ad libitum*, were provided in powder (TestDiet Inc., Richmond, IN) in a large bowl and contained a standard vitamin and mineral mix with all essential nutrients. After 4 weeks of feeding with RD or FO diet, a subgroup of rats was exposed to mild fluid percussion injury (FPI). After consumption of the same diet for 1 week post-injury, rats ($n = 6$–8 within each group) were killed by decapitation. The brains were rapidly dissected and frozen on dry ice, and stored at −70°C until use for biochemical analyses including ELISA, western blot, and measurement of oxidized protein levels by Oxyblot. For immunohistochemistry, the rats ($n = 4$ within each group) were transcardially perfused with 400 mL of 4% paraformaldehyde and 100 mL of 30% sucrose. The fixed brains were then removed and stored at −70°C until use. All experiments were performed in accordance with the *United States National Institute of Health Guide for the Care and Use of Laboratory Animals* and were approved by the University of California at Los Angeles Chancellor's Animal Research Committee. The suffering and number of animals used were minimized.

Fluid Percussion Injury

The injury was performed as previously described (Wu et al., 2003). In brief, with the aid of a microscope (Wild, Heerburg, Switzerland) a 3.0-mm diameter craniotomy was made 3.0 mm posterior to bregma and 6.0 mm lateral (left) to the midline with a high-speed drill (Dremel, Racine, WI). A plastic injury cap was placed over the craniotomy with silicone adhesive and dental cement. When the dental cement hardened, the cap was filled with 0.9% saline solution. Anesthesia was discontinued and the injury cap was attached to the fluid percussion device. At the first sign of hind-limb withdrawal to a paw

pinch, a mild fluid percussion pulse (1.5 atm) was administered. Sham animals underwent an identical preparation with the exception of the lesion. Immediately upon responding to a paw pinch, anesthesia was restored and the skull was sutured. Neomycin was applied on the suture and the rats were placed in a heated recovery chamber for approximately an hour before being returned to their cages.

Measurement of Oxidized Proteins

The amounts of oxidized proteins containing carbonyl groups were measured by using an Oxyblot kit (Intergen, Purchase, NY). Briefly, the protein sample (10 μg) from hippocampal tissue was reacted with 1 $\times$ dinitrophenylhydrazine (DNPH) for 15 min, followed by neutralization with a solution containing glycerol and β-mercaptoethanol. These samples were electrophoresed on an 8% polyacrylamide gel and electrotransferred to a nitrocellulose membrane. After blocking, membranes were incubated overnight with a rabbit anti-DNPH antibody (1:150) at 4°C, followed by incubation in goat anti-rabbit (1:300) for 1 h at room temperature. After rinsing with buffer, the immunocomplexes were visualized by chemiluminescence using the ECL kit (Amersham Pharmacia Biotech Inc., Piscataway, NJ) according to the manufacturer's instructions. The Oxyblot bands were all grouped together in each group and then analyzed by NIH image software.

Cognitive Testing

The cognitive testing was performed in a water maze as described previously (Molteni et al., 2002; Wu et al., 2003) at day 5, 6, and 7 after surgery. The swimming pool (130 cm diameter, 50 cm height) was divided into four quadrants delimiting separate zones. The quadrant where the escape platform (12 cm diameter) was located in a fixed position with 2 cm under the water surface was defined as target zone; the other three quadrants were left, right and opposite zone. The water (22 $\pm$ 2°C) was made opaque with white nontoxic biodegradable dye to prevent the rats from seeing the platform. The rats were trained in the water maze with 10 consecutive trials per day for 3 days. The rats were placed into the tank facing the wall from one of the four equally spaced start locations that were randomly changed every trial. The spatial cues for reference around the pool were maintained constant throughout the duration of the experiment. Each trial lasted until the rat found the platform or for a max of 2 min. If the rat failed to find the platform in the allocated time, it was gently placed on the platform. At the end of each trial, the animals were allowed to rest on the platform for 1 min. The behavioral variables including swimming distance (cm) and spent time (s) were recorded with the computer-controlled Smart Video tracking system (San Diego Instruments, San Diego, CA).

ELISA

Hippocampal tissue was homogenized in a lysis buffer containing 137 mM NaCl, 20 mM Tris-HCl pH 8.0, 1% NP40, 10% glycerol, 1 mM PMSF, 10 μg/mL aprotinin, 0.1 mM benzethonium chloride, 0.5 mM sodium vanadate. The homogenates were then centrifuged, the supernatants were collected and total protein concentration was determined according to MicroBCA procedure (Pierce, Rockford, IL), using bovine serum albumin as standard. BDNF protein was quantified using an enzyme-linked immunosorbent assay (ELISA) kit (BDNF Emax ImmunoAssay System kit, Promega Inc., Madison, WI) according to manufacturer's protocol.

Western Blot

The total proteins from hippocampal tissue were extracted as described above. Synapsin I and CREB were analyzed by western blot. Briefly, protein samples were separated by electrophoresis on an 8% polyacrylamide gel and electrotransferred to a nitrocellulose membrane. Non-specific binding sites were blocked in TBS, overnight at 4°C, with 2% BSA and 0.1% Tween-20. Membranes were rinsed for 10 min in buffer (0.1% Tween-20 in TBS) and then incubated with anti-actin, anti-synapsin I (1:2000, Santa Cruz Biotechnology, Santa Cruz, CA), followed by anti-goat IgG horseradish peroxidase-conjugate (Santa Cruz Biotechnology); anti-CREB (1:1000; Cell Signaling Technology, Beverly, MA), followed by anti-rabbit IgG horseradish peroxidase-conjugate (Santa Cruz Biotechnology). After rinsing with buffer, the immunocomplexes were visualized by chemiluminescence using the ECL kit (Amersham Pharmacia Biotech Inc., Piscataway, NJ) according to the manufacturer's instructions. The film signals were digitally scanned and then quantified using NIH Image software. Actin was used as an internal control for western blot such that data were standardized according to actin values.

Immunohistochemistry

Serial coronal sections (25 μm) were cut on a cryostat, mounted to gelatin-coated slides and processed for immunohistochemistry, as previously described (Gomez-Pinilla et al., 2001). A 1:1000 dilution was used for the rabbit polyclonal anti-BDNF (Chemicon International Inc., Temecula, CA). Immunohistochemistry controls were performed by omission of the primary antibody. The

results of immunohistochemistry controls were negative as no staining was observed in cell structures.

Statistical Analysis

Actin was employed as internal standard for western blot. The RD rats with sham surgery were regarded as experimental controls for comparisons with other experimental groups. For Western blot, the values were expressed as a ratio of actin value and then converted to percent of Sham-RD group as presented in bar figures and represented the mean ± SEM. The data were analyzed by ANOVA followed by Fisher's protected least significance *post hoc* test. Statistical differences were considered significant at $p < 0.05$.

RESULTS

Omega-3 Fatty Acid Supplementation Compensates for Cognitive Impairment Associated with TBI

We have previously shown that TBI impairs learning ability in rats (Wu et al., 2003). To determine whether omega-3 fatty acids in the diet can provide protection against learning impairment after TBI, we assessed the effects of FO supplementation on intact rats and rats undergoing FPI. The learning performance was assessed using the Morris water maze. The results demonstrated that TBI-RD rats performed worse than Sham-RD rats as evidenced by longer escape latency to locate the platform in the Morris water maze (Fig. 1A). In contrast, TBI rats fed the FO supplemented diet showed significant improvement in their learning ability with latency to find the platform similar to that of Sham-RD animals (Fig. 1A). There was no significant difference in swimming speed across the different experimental groups (Fig. 1B).

Omega-3 Fatty Acid Supplementation Normalizes Levels of BDNF, Synapsin I, and CREB after TBI

Robust evidence implicates BDNF in maintaining synaptic plasticity and cognition (Bolton et al., 2000; Hariri et al., 2003; Kang and Schuman, 1996; Thoenen, 1995). Therefore, we have focused on the action of BDNF as a manipulating factor to counteract the learning impairment observed after TBI. Levels of BDNF were measured in the hippocampus of four experimental groups: Sham-RD, TBI-RD, Sham-FO, and TBI-FO. We have previously shown that TBI significantly decreases hippocampal levels of BDNF in rats consuming a regular diet (Wu et al., 2003). The current results showed that omega-3 fatty acids supplementation normalizes BDNF levels in the hippocampus of TBI rats (Fig. 2A). Immunohistochemistry showed relatively normal BDNF immunostaining in the cornus amonus 3 (CA3) and the dentate gyrus (DG) of the hippocampal formation of TBI rats supplemented with FO (Fig. 2B).

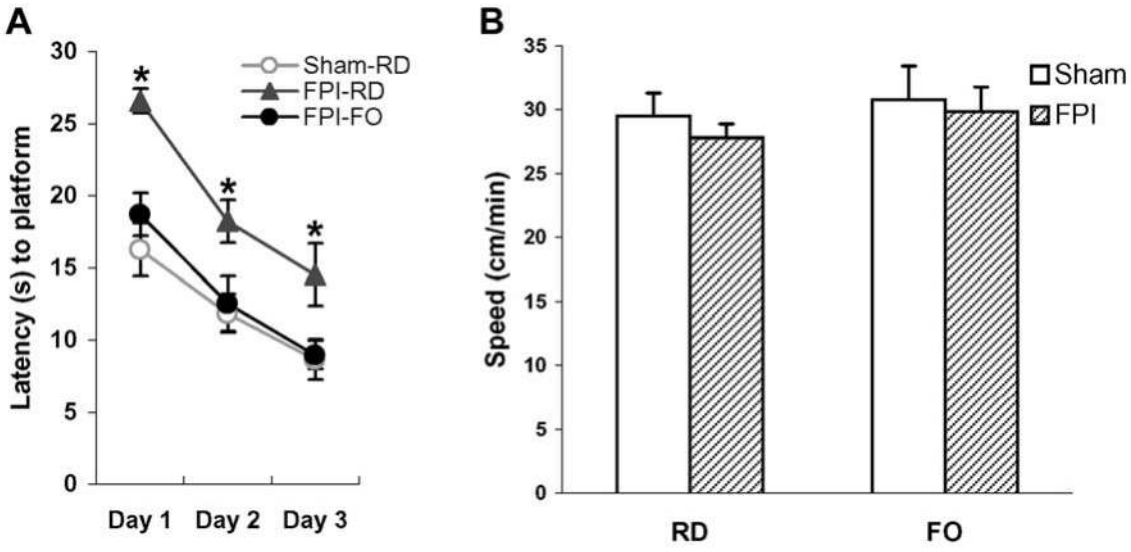
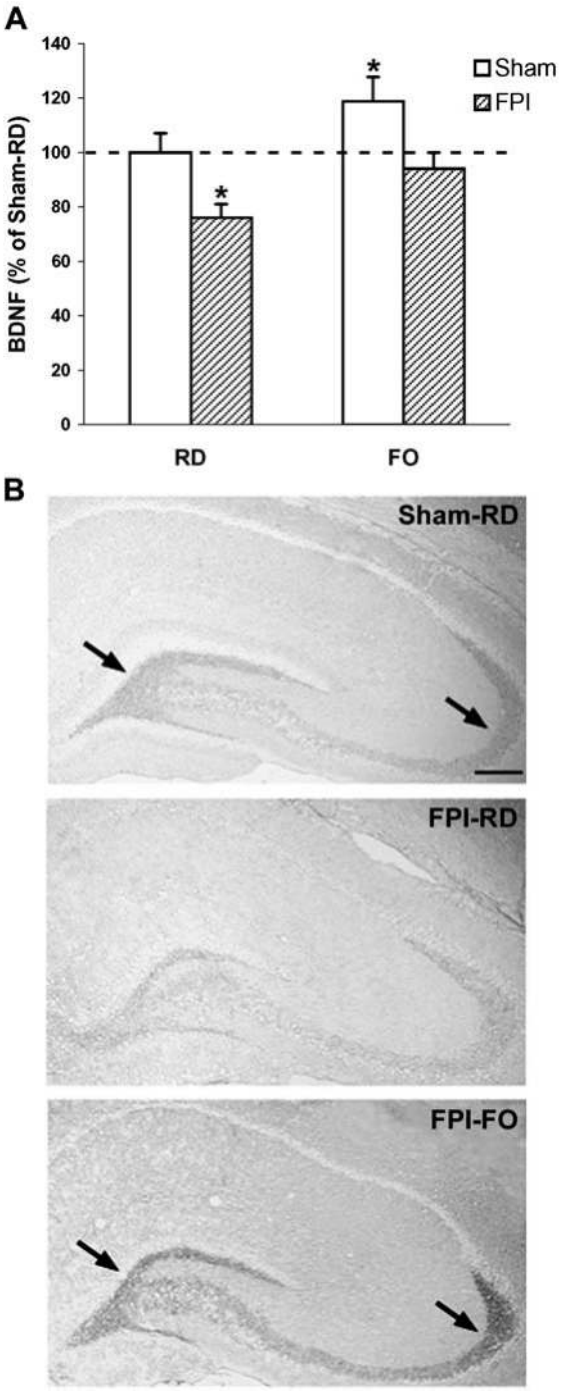


FIG. 1. Dietary omega-3 fatty acids supplementation provides protection against deficit in learning ability resulting from FPI. Learning performance was scored as average of escape latencies (s) to locate the platform in the Morris water maze. (**A**) The escape latency was significantly longer in FPI-RD rats compared with Sham-RD animals. FPI rats supplemented with omega-3 fatty acids showed escape latencies similar to that of Sham-RD rats. *$p < 0.05$. (**B**) There was no significant difference in swimming speed across the different experimental groups.

BDNF facilitates synaptic transmission and regulates gene expression through activation of synapsin I and CREB (Finkbeiner, 2000; Jovanovic et al., 1996; Wang et al., 1995; Ying et al., 2002). Our previous report indicates that TBI may affect cognitive ability by compromising some of the action of BDNF on synaptic plasticity (Wu et al., 2003). To evaluate whether omega-3 fatty acids supplemented in the diet could protect against disruption in molecular systems that maintain synaptic plasticity after TBI, we measured the protein expression of synapsin I and CREB in the hippocampus by Western blot analysis. The results showed that dietary omega-3 fatty acids supplementation normalized levels of synapsin I (Fig. 3A,B) and CREB (Fig. 4A,B) in the hippocampus of TBI rats.



Omega-3 Fatty Acid Supplementation Reduces Oxidative Damage in TBI Animals

Oxidative damage was assessed using Western blot analysis of DNPH-derivatized carbonyl groups on oxidized proteins. A representative example of an Oxyblot gel is shown in Figure 5A. The oxidized protein levels were significantly increased in TBI-RD animals relative to Sham-RD rats (Fig. 5B). However, the TBI animals fed the diet supplemented with FO had significant lower levels of oxidized proteins compared with TBI-RD, Sham-RD, and Sham-FO animals (Fig. 5B).

DISCUSSION

Our results demonstrate that supplementation of omega-3 fatty acids in the diet normalizes hippocampal levels of BDNF and its downstream effectors on synaptic plasticity synapsin I and CREB, after experimental TBI. Restoration in levels of these molecular systems was associated with a normalized spatial learning ability in the Morris water maze. These findings suggest that omega-3 fatty acid–enriched dietary supplements can be a potent therapeutic agent for reducing the deleterious effects of TBI on synaptic plasticity and cognition. In addition, the finding that omega-3 fatty acids reduced oxidative damage as a result of TBI appear to reveal a general benevolent effect of omega-3 fatty acids on

FIG. 2. Omega-3 fatty acids normalized BDNF levels in the hippocampus of FPI rats measured using ELISA. (**A**) FPI reduced BDNF levels, and this effect was reversed by FO dietary supplementation. FO supplementation increased BDNF levels in intact rats (Sham-FO). The values were converted to percent of Sham-RD (mean ± SEM). $*p < 0.05$. (**B**) Immunohistochemistry shows that BDNF was predominantly distributed along the mossy fiber system that runs between CA3 and the dentate gyrus (DG), and in the molecular layer of the DG of the hippocampal formation. The omega-3 fatty acids supplementation prevented the reduction in BDNF immunoreactivity in animals receiving FPI.

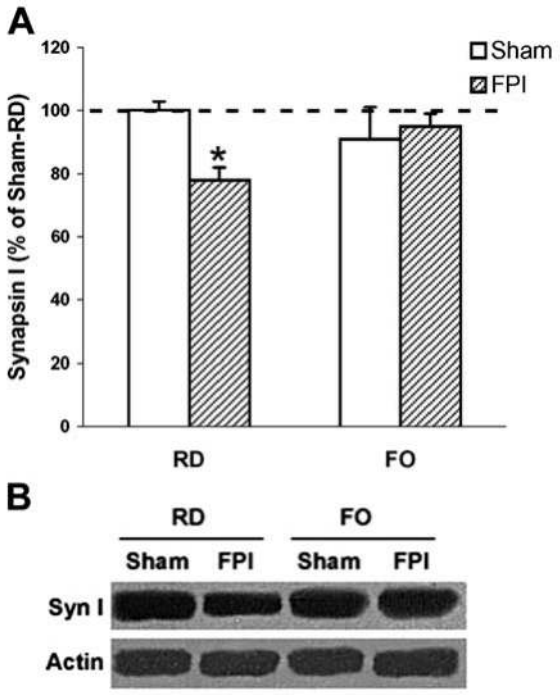


FIG. 3. Omega-3 fatty acids reverse the FPI-elicited reduction of synapsin I in the hippocampus. (**A**) Western blot analysis using actin as standard control showed that FPI reduced synapsin I levels, and that these effects of FPI were reversed by FO supplementation. FO supplementation did not affect synapsin I levels in intact rats (Sham-FO). Protein values were converted to percent of sham (mean ± SEM). $*p < 0.05$. (**B**) Representative immunoblot sample gels for synapsin I in each experimental group.

mechanisms that maintain neuronal function and plasticity after TBI.

Omega-3 Fatty Acids May Affect Cognition by Modulating the BDNF System

Our finding that supplementation of omega-3 fatty acids normalizes the protein levels of BDNF after TBI suggests that BDNF mediates the beneficial effects of omega-3 fatty acids on cognitive function. We have recently shown that TBI reduces BDNF, synapsin I, and CREB, with subsequent effects on cognitive function (Wu et al., 2003). The question is: How can omega-3 fatty acids compensate for cognitive decline resulting from TBI? It is well accepted that BDNF modulates synaptic plasticity (Bolton et al., 2000; Hariri et al., 2003; Kang and Schuman, 1996; Thoenen, 1995), and is required for normal learning in the Morris water Maze (Mu et al., 1999). BDNF can facilitate synaptic transmission and regulate gene expression through activation of synapsin I and CREB (Finkbeiner, 2000; Jovanovic et al., 1996; Wang et al., 1995; Ying et al., 2002). Our results showed that omega-3 fatty acids normalize the protein levels of synapsin I and CREB in TBI rats. Since BDNF and its downstream effectors synapsin I and CREB are involved in learning and memory events, our findings suggest that supplementation of omega-3 fatty acids in the diet may provide protection against learning disability after TBI via upregulation of these molecular systems (Fig. 6).

It is notable that FO supplementation increased BDNF but did not affect cognitive function in intact rats. It is possible that slight changes in BDNF may not significantly affect cognition under normal conditions. It seems likely, however, that under pathological weakness small decreases in BDNF can be a factor to further deteriorate cognitive function. This eventual possibility emphasizes the necessity to use therapeutic means, such as dietary

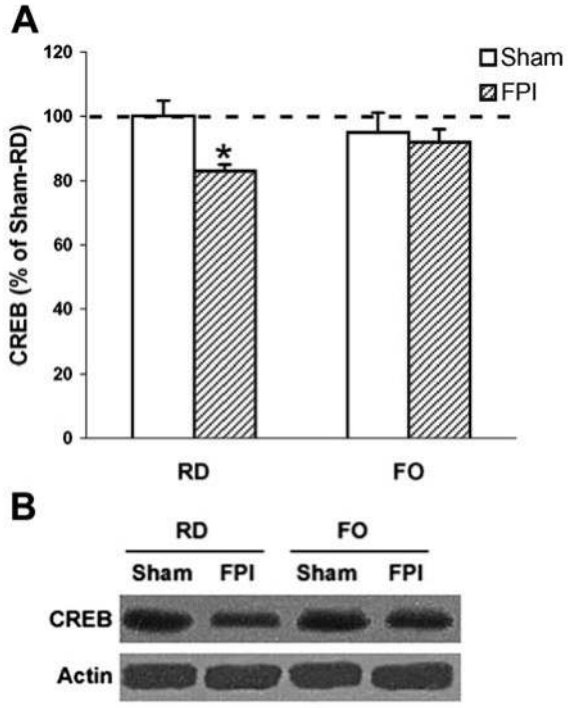


FIG. 4. Omega-3 fatty acids dietary supplementation reverses the FPI-elicited reduction of CREB in the hippocampus. (**A**) The level of CREB was determined by western blot analysis using actin as a standard control. Results show that FPI decreased CREB, and that this effect was reversed by FO supplementation. FO supplementation did not affect CREB levels in intact rats (Sham-FO). The values were converted to percent of sham-RD (mean ± SEM). $*p < 0.05$. (**B**) Representative immunoblot gels for synapsin I in each experimental group.

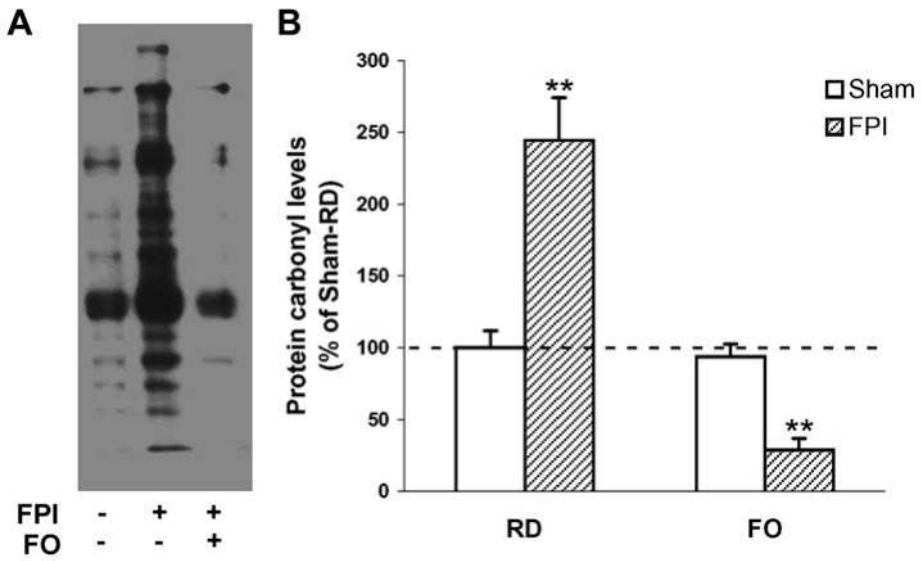


FIG. 5. Measurements of oxidized protein levels in the hippocampus. The oxidized protein levels were determined by Oxyblot kit. (**A**) Representative sample of Oxyblot bands. (**B**) FPI resulted in higher oxidized protein levels compared with Sham-RD animals, whereas FO feeding markedly reduced the FPI-induced elevation in protein carbonyl levels. FO supplementation did not affect oxidized protein levels in intact rats (Sham-FO). The values were converted to percent of Sham-RD (mean ± SEM). $^{**}p < 0.01$.

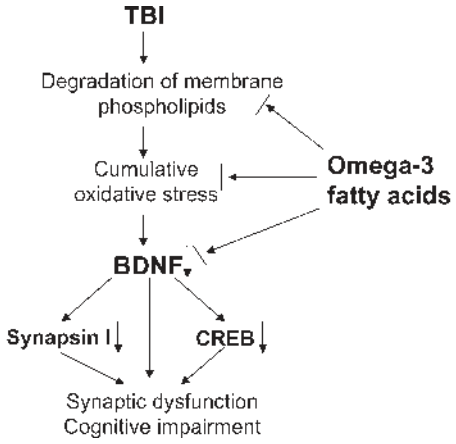


FIG. 6. Possible mechanisms underlying the effects of omega-3 fatty acids supplementation on restoring neural plasticity after TBI. TBI results in degradation of membrane phospholipids, leading to cumulative oxidative stress, which in turn may cause reduction in BDNF and its synaptic plasticity effectors synapsin I and CREB. These alterations may underlie synaptic dysfunction and cognitive impairment resulting from TBI. Omega-3 fatty acids supplementation may prevent the degradation of membrane phospholipids and subsequent cumulative oxidative stress. Omega-3 fatty acids can also contribute to normalized levels of BDNF, synapsin I, and CREB. The action of oxidative stress may also affect the regulation of the BDNF system and synaptic plasticity.

supplementation of FO, to maintain normal levels of BDNF under challenging conditions (Molteni et al., 2002, 2004; Wu et al., 2003, 2004).

Oxidative Stress May Be an Intermediate Step by which TBI and Dietary Factors Modulate Synaptic Plasticity and Cognition

We detected markedly elevated levels of protein carbonyl formation in TBI animals using a convenient Western blot analysis of DNPH derivatized carbonyls. Supplementation of omega-3 fatty acids in the diet, however, dramatically reduced the elevated protein carbonyls, which is consistent with the known antioxidant activity of DHA (Hashimoto et al., 2002; Hossain et al., 1999). For example, DHA has shown anti-oxidant capacity in the aging brain with subsequent effects on cognition (Hashimoto et al., 2002; Hossain et al., 1999). It is possible that the potential anti-oxidant action of DHA in TBI may be achieved using mechanisms that maintain synaptic plasticity. It has been shown that TBI can result in cumulative ROS (Marklund et al., 2001; Paolin et al., 2002; Pratico et al., 2002), which may be associated with reduction of BDNF (Wu et al., 2003, 2004). Thus, DHA may help to counteract elevated levels of ROS with subsequent effects on the action of BDNF on synaptic plasticity and cognition after TBI. Although the major com-

ponents of FO in our study are DHA and EPA, it is likely that the beneficial effects of FO supplementation are attributable to DHA. This possibility is supported by studies showing that (1) EPA is absent in normal brain (Kitajka et al., 2002); (2) EPA can be converted to DHA in the body (Pawlosky et al., 2001); and (3) EPA cannot cross the blood–brain barrier. However, a direct link between DHA and the observed findings in our study need to be further investigated by using pure DHA in the diet.

It is known that DHA affects LTP, one of the most impressive forms of synaptic plasticity (Bliss and Collingridge, 1993) and a biological substrate for learning and memory (Moser et al, 1998). Emerging evidence indicates that dietary omega-3 fatty acids can restore the DHA in the neuronal membrane and reverse the age-related synaptic dysfunction such as impairment in LTP (McGahon et al., 1999). Indeed, DHA supplemented in the diet can improve learning ability (Lim and Suzuki, 2001; Suzuki et al., 1998) and enhance long-term memory in both young and old animals (Gamoh et al., 1999, 2001; Lim and Suzuki, 2000), and can reduce cognitive decline during aging and AD (Hashimoto et al., 2002). Our findings provide novel evidence suggesting that the action of omega-3 fatty acids (i.e., DHA) in reducing cognitive impairment after TBI are associated with restoration of molecular systems that serve synaptic plasticity. Our results also suggest that this diet can exert its action by diminishing cumulative ROS.

Omega-3 Fatty Acids Can Help the TBI Brain by Restoring Membrane Integrity

Emerging evidence indicates that TBI can lead to degradation of membrane phospholipids (PLs), resulting in accumulation of reactive oxygen species. It is possible that these events can result in perturbations of synaptic plasticity (Fig. 6). It has been known that synaptic membranes phospholipids are preferentially enriched in omega-3 fatty acids, especially DHA. TBI can result in acute and long-lasting perturbation in brain phospholipid metabolism (Homayoun et al., 1997; Marklund et al., 1997). Degradation of membrane PLs, a well-known phenomenon in acute brain injuries (Homayoun et al., 1997; Marklund et al., 1997), is thought to underlie the disturbance of cellular membrane functions, contributing to secondary neuronal injury (Farooqui and Horrocks, 1994). Synaptic terminals show a high activity in phospholipid-hydrolyzing enzymes (i.e. PLA_2, PLC; Bazan et al., 1995), which can be intensified after TBI (Shohami et al., 1989; Wei et al., 1982). Activation of PLA_2 and PLC may hydrolyze PLs, resulting in cumulative oxidative stress and subsequent neuronal dysfunction. Thus, TBI-induced PL degradation and subsequent oxidative damage may contribute to impairment in cognition and neuroplasticity (Fig. 6). The overall evidence suggests that supplementation of omega-3 fatty acids (i.e., DHA) in the diet may help the TBI brain preserve synaptic membrane integrity and fluidity, which are crucial factors for maintenance of vital cellular function.

CONCLUSION

Our findings demonstrate that omega-3 fatty acids supplementation can restore cognitive function after TBI, and that this may be achieved by normalizing the action of BDNF on synaptic plasticity using synapsin I and CREB. Results also show that this diet can provide protection against oxidative damage after TBI, which may also influence synaptic plasticity and cognition. These results suggest that dietary omega-3 fatty acids supplementation has a therapeutic potential to reduce the deleterious effects of TBI and perhaps other insults on synaptic plasticity and cognitive function.

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Address reprint requests to:
Fernando Gomez-Pinilla, Ph.D.
Department of Physiological Science
621 Charles E. Young Dr.
Los Angeles, CA 90095

E-mail: fgomezpi@ucla.edu