Preventive Medicine 54 (2012) S103–S108

Contents lists available at SciVerse ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

n−3 fatty acids prevent impairment of neurogenesis and synaptic plasticity in B-cell activating factor (BAFF) transgenic mice

Rosalia Crupi [a], Marco Cambiaghi [a], Richard Deckelbaum [b,c], Inge Hansen [c], Janet Mindes [e], Edoardo Spina [d], Fortunato Battaglia [a,e,f,*]

[a] Department of Physiology and Pharmacology, CUNY Medical School, New York, NY, USA
[b] Institute of Human Nutrition, College of Physicians and Surgeons, Columbia University, New York, NY, USA
[c] Department of Medicine and Pediatrics, College of Physicians and Surgeons, Columbia University, New York, NY, USA
[d] Department of Clinical and Experimental Medicine and Pharmacology, University of Messina, Italy
[e] Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York, NY, USA
[f] Department of Physiology, New York College of Podiatric Medicine, New York, NY, USA

ARTICLE INFO

Available online 28 December 2011

Keywords:
n−3 fatty acid
Neurogenesis
BAFF
Dentate gyrus
LTP

ABSTRACT

Objective. Autoimmune-prone B-cell activating factor transgenic mice, a mouse model of systemic lupus erythematosus and Sjögren's syndrome exhibit neuroinflammation, anxiety-like phenotype, deficit in adult hippocampal neurogenesis and impaired neurogenesis-dependent and neurogenesis-independent dentate gyrus long-term potentiation. Given that n−3 polyunsaturated fatty acids regulate hippocampal plasticity and inflammatory responses, we investigated whether n−3 polyunsaturated fatty acids-enriched diet might prevent age-dependent hippocampal changes in B-cell activating factor transgenic mice.

Methods. B-cell activating factor transgenic mice were fed for 12 weeks with either n−3 polyunsaturated fatty acids-enriched or control diet and we tested the effect of this dietary supplementation on hippocampal inflammation, progenitor cell proliferation and neurogenesis-dependent and neurogenesis-independent long-term potentiation.

Results. Dietary supplementation with n−-3 polyunsaturated fatty acids significantly decreased hippocampal microglial activation and increased the density of bromodeoxyuridine and doublecortin-positive newly-formed cells in the subventricular zone of hippocampus. Furthermore, B-cell activating factor transgenic mice fed with n-3 polyunsaturated fatty acids-enriched diet displayed normal long-term potentiation at the medial perforant pathway/dentate gyrus connections.

Conclusions. The results indicate that n-3 fatty acids prevent neuroinflammation and deficits of hippocampal plasticity in B-cell activating factor transgenic mice and suggest that increased n-3 fatty acids intake might represent a potential therapeutic option to prevent neuropsychiatric symptoms associated with autoimmune diseases.

Introduction

Systemic lupus erythematosus (SLE) and Sjögren's syndrome (SjS) are prototypic autoimmune diseases characterized by a loss of immunologic tolerance, production of auto-antibodies and inflammation eventually leading to multiple organ damage (Croker and Kimberly, 2005). Several cytokines have been involved in the pathogenesis of these disorders. B-cell activating factor (BAFF) is a powerful modulator of B-cell activity (Mackay and Schneider, 2009). BAFF blood levels are increased in patients with autoimmune diseases such as SLE and SjS and the neutralization of this cytokine is now a promising approach to prevent the development of these conditions (Melchers, 2003). BAFF transgenic (Tg) mice develop an SLE and secondary SjS-like phenotype (Mackay et al., 1999) (Groom et al., 2002). Furthermore, BAFF Tg mice exhibit age-dependent abnormal emotional behavior associated with brain inflammation, decreased adult hippocampal neurogenesis and dentate gyrus (DG) deficit in neurogenesis-dependent and neurogenesis-independent long-term potentiation (LTP) (Crupi et al., 2010). Given that antidepressant treatments modulate hippocampal plasticity and neuroinflammation (Krishnan and Nestler, 2010) (Bianchi et al., 1994; Mackay et al., 2009; Chung et al., 2011), it is likely that new therapeutic treatments for neuropsychiatric symptoms associated with autoimmune diseases might affect these hippocampal biomarkers in BAFF Tg mice.

Consumption of n−3 polyunsaturated fatty acids (n−3 PUFAs) modulates inflammation, neurogenesis and hippocampal plasticity

* Corresponding author at: New York College of Podiatric Medicine (NYCPM), Department of Physiology-Neuroscience, 53 East 124th Street, Room 509, New York, NY 10035, USA. Fax: +1 212 410 0940.
E-mail address: fbattaglia@nycpm.edu (F. Battaglia).

0091-7435/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.ypmed.2011.12.019

making these fatty acids attractive candidates for prevention and amelioration of neuropsychiatric symptoms of several autoimmune diseases (Ma et al., 2008; Robson et al., 2008; Yamashima, 2008; He et al., 2009; Kashiyae et al., 2009; Venna et al., 2009; Ma et al., 2010; Osumi, 2010). Furthermore, it has been proposed that dietary factors may contribute to the etiology and progression SLE and SjS syndrome, and that nutritional intervention may modify the severity of pathological abnormalities (Lefkowith and Klahr, 1996; Simopoulos, 2002; Cermak et al., 2003; Pestka, 2010). A previous report indicates that n−3 PUFA-supplemented diet has positive effects on autoimmune-prone NZB/W female mice by regulating the activity of antioxidant enzymes (Bhattacharya et al., 2003). To date, there are no studies that explored the role of n−3 PUFA on hippocampal progenitor cell proliferation and synaptic plasticity in BAFF Tg mice.

The present study was designed to determine whether a diet supplemented with n−3 fatty acid leads to prevention or attenuation of age-dependent hippocampal abnormalities in BAFF Tg mice. Therefore, we investigated the effects of the interventions on hippocampal inflammation, progenitor cell proliferation and DG LTP.

Materials and methods

Animals

8 week-old BAFF Tg and wild-type (WT) mice on a C57BL/6 background (Mackay et al., 1999) were used in the experiments. Mice were kindly provided by Dr. Linda Spatz at CCNY and were maintained under 12:12 light–dark cycle in a temperature (21 °C ± 1 °C) and humidity (50% ± 5%) controlled room. All procedures were approved by the Institutional Laboratory Animal Care and Use Committee at the City College of New York.

Prior to study commencement, both WT and BAFF Tg had free access to a standard rodent chow. At beginning of the study, (8 week-old mice, prior to the appearance of the behavioral and hippocampal abnormalities) mice were provided with 12 weeks *ad libitum* access to control diet or diet supplemented with PUFA. PUFA-supplemented diet contained both n−6 and n−3 PUFA whereas control diet lacked n−3 PUFA (Table 1). Mice were randomized into 3 groups: *group 1*, WT treated with control diet, *group 2*, BAFF Tg treated with control diet; *group 3*, BAFF Tg treated with n−3 PUFA-supplemented diet.

Diets

N−3 PUFA-enriched and control diets were prepared by Harlan Tekland (Madison, WI) and were stored in vacuum bags to reduce PUFA oxidation. The fatty acid composition of the diets is presented in Table 1. As previously reported, this n−3 PUFA-supplemented diet modulates emotional behaviors, neurogenesis and synaptic plasticity in mice (Venna et al., 2009).

CD68 immunostaining

CD68 is a marker of neuroinflammation (activated microglia). Tissue sections (40 μm) were processed using a previously described immunohistochemical procedure (Grider et al., 2006). An unbiased, semi-quantitative analysis of the diaminobenzidine (DAB) stained cells in the hippocampus was then performed using ImageJ program (National Institute of Health, Bethesda, MA, USA). Three fields (CA1, CA3 and DG) were randomly captured in each image. The measurements obtained in each hippocampal regions were averaged to obtain an estimate of hippocampal inflammatory response. In each animal, three consecutive slides (starting from brain slices at the levels of Bregma—0.82 mm) were stained and analyzed. Data are expressed as number of particle/area ± SE (Crupi et al., 2010).

Table 1
Fatty acid composition (%) of control and n−3 PUFA-enriched diet. New York, USA, 2009.

Fatty acids	n−3 PUFA diet	Control diet
C16:0 palmitic	0.63	2.10
C18:0 stearic	0.21	0.70
C18:1 ω9 oleic	3.15	2.31
C18:2 ω6 linoleic	1.61	1.89
C18:3 ω3 alpha-linolenic	0.70	0.0
C18:3 ω6 gamma-linolenic	0.21	0.0
C18:4 ω3 stearidonic	0.14	0.0
C20:4 ω6 arachidonic	0.035	0.0
C20:5 ω3 eicosapentaenoic	0.35	0.0
C22:6 ω3 docosahexaenoic	0.14	0.0

Hippocampal progenitor cell proliferation

To investigate the effect of n−3 PUFA-supplemented diet on hippocampal adult neurogenesis, the incorporation of thymidine analogue 5-bromo-2′-deoxyuridine (BrdU) in proliferating cells was evaluated. Mice were administered intraperitoneally with 150 mg/kg BrdU dissolved in saline (Sigma-Aldrich, St. Louis, MO, USA). Two hours after the injection, mice were anesthetized with sodium pentobarbital (30 mg/kg, Sigma-Aldrich, St. Louis, MO, USA), sacrificed and transcardially perfused with ice cold 0.1-mol/L PBS (pH 7.4), followed by ice cold 4% paraformaldehyde in 0.1-mol/L PB. 35 μm thick brains slices were collected for immunocytochemistry through the entire hippocampus. The staining was visualized with DAB. Briefly, sections were boiled in citric acid (pH 6.0) for 5 min, rinsed with PBS, treated with 0.01% trypsin in Tris/CaCl2 for 10 min, incubated for 30 min with 2 N HCl and blocked with 5% NGS. Sections were first incubated overnight with anti-mouse BrdU (1:100) and then were incubated for 1 h with secondary antibody (1:200 biotinylated goat anti-mouse). Sections were developed using the DAB kit (Vector, CA, USA). BrdU labeling was quantified according to a method previously described (Malberg et al., 2000).

Doublecortin staining

For Doublecortin (DCX) staining sections were rinsed in PBS, treated with 1% H_2O_2 in 1:1 PBS and methanol, incubated in 10% normal donkey serum and 0.3% Triton X-100 for 30 min, incubated overnight at 4 °C in primary antibody for doublecortin (goat; 1:500; Santa Cruz Biotechnology, Santa Cruz, CA, USA). The secondary antibody was biotinylated donkey anti-goat (1:500) (Jackson ImmunoResearch, PA, USA) DCX+ cells were subcategorized according to their dendritic morphology: DCX+ cells with no tertiary dendritic processes and DCX+ cells with complex, tertiary dendrites. Sholl analysis was performed on DCX^+ cells with tertiary dendrites ($n = 10$ cells per brain) using Neurolucida (Microbrightfield, Williston, Vermont) and the dendritic length and number of intersections used were calculated using NeuroExplorer (Microbrightfield, Williston, Vermont). All samples were number coded, and analysis was done blind to genotype (Wang et al., 2008). Images were collected with a Zeiss (Oberkochen, Germany) Axioplan-2 upright microscope.

Electrophysiology

Transverse hippocampal slices were prepared from WT and BAFF Tg mice and maintained in an interface chamber at 32 °C and perfused with oxygenated artificial cerebrospinal fluid containing 119 mM NaCl, 2.3 mM KCl, 1.3 mM MgSO4, 2.5 mM CaCl2, 26.2 mM NaHCO3, 1 mM NaH2PO4, and 11 mM glucose. Slices were allowed to equilibrate for 2 h before recording. The medial perforant pathway (MPP) was identified by assessing paired-pulse inhibition of the MPP/DG synaptic connection. Field excitatory postsynaptic potentials (fEPSP) were recorded in the molecular layer above the upper blade of the DG by using a glass capillary microelectrode filled with artificial cerebrospinal fluid (tip resistance 1–3 MΩ). Basal synaptic transmission was monitored every 30 s with a stimulus intensity that produced a third maximal response. Neurogenesis-dependent long-term potentiation (artificial cerebrospinal fluid [ACSF]-LTP) was induced with four trains of 1 s each, 100 Hz within the train, repeated every 15 s. Neurogenesis-dependent LTP was induced in the presence of 50 μmol/L picrotoxin (Sigma, St. Louis, Missouri) in the artificial cerebrospinal fluid (PICRO-LTP). Responses were recorded every minute for 60 min after LTP induction (Crupi et al., 2010).

Data analysis

All values are expressed as mean ± standard (S.E.M.). The results were analyzed by analysis of variance (ANOVA), followed by a Fisher's post-hoc test. The level of significance was set to $P<0.05$.

Results

Neuroinflammation

To investigate the mouse genotype effect on hippocampal neuroinflammation, CD68 number of particle/area in WT and BAFF Tg mice fed with control diet were compared. The results confirm our earlier report and indicate an age-dependent development on hippocampal inflammation in BAFF Tg mice ($F_{(1,8)}=27.4$, $P=0.012$). n−3 PUFA prevented the development of microglial proinflammatory reaction in BAFF Tg mice ($F_{(1,8)}=4.3$, $P=0.4$). (Figs. 1A and B).

Progenitor cell proliferation

Progenitor cell proliferation was assessed by using BrdU and DCX immunohistochemistry (Figs. 2A, B). BrdU is incorporated into the DNA of proliferating cells in the S phase of the mitotic cycle and selectively labels dividing cell. Stereological analysis revealed that there was a significant decrease in the number of BrdU+ cells in the DG sections from BAFF Tg mice treated with control diet compared with WT mice (WT-control: 2,211.3±43.3; BAFF Tg-control: 2,005.7±38.4, $F_{(1,8)}=24.8$, $P=0.001$). On the contrary, n−3 PUFA-supplemented diet increased the number of $BrdU^+$ cells in the granule cell layer (GCL) and prevented age-dependent deficit in progenitor cell proliferation in BAFF Tg mice (BAFF Tg-PUFA: 2,159.6±40.5, $F_{(1,8)}=3.5$, $P=0.1$) (Fig. 2B).

Furthermore, ANOVA revealed that BAFF Tg mice fed with control diet showed a decreased number of total DCX^+ cell (WT-control: 2,454.2±47.5; BAFF Tg-control: 2,231.6±50.3, $F_{(1,8)}=12.4$, $P=0.01$). n−3 PUFA-supplemented diet prevented this age-dependent deficit (BAFF Tg-PUFA: 2,553.5±42.7, $P>0.05$) (Fig. 2C).

Neurogenesis-dependent and independent LTP in MPP/DG connections

To study basal synaptic transmission and LTP in hippocampus a series of electrophysiological recordings in hippocampal slices were obtained from WT and BAFF Tg mice. fEPSPs were obtained stimulating the MPP and recording in GCL in DG. To determine the effects of diets on basal synaptic transmission we first plotted fEPSP slopes against various stimulation intensities. No significant differences in input–output curves were obtained between groups ($P>0.05$). Similarly, no between group differences in PPI were observed ($P>0.05$) (Figs. 3A and B).

Next the neurogenesis-independent LTP was examined. This form of DG LTP is obtained in the presence of the γ-aminobutyric acid (GABA) antagonist Picrotoxin (PICRO) and is induced when GABAergic inputs to mature granule cells are inhibited. BAFF Tg-control mice showed a significant deficit in PICRO-LTP. The amount of LTP obtained 60 min after tetanus was 165.6±8.8% in WT-Control mice and 134.2±6.4% in BAFF Tg-Control mice ($F_{(1,8)}=18.2$, $P<0.01$). n−3 PUFA-supplemented diet prevented this deficit (BAFF Tg-PUFA: 161.3±6.98%, 60 min after tetanus ($F_{(1,8)}=4.1$, $P=0.2$) (Fig. 3C).

Tetanic stimulation of the MPP/DG path in the absence of Picrotoxin elicits a weak LTP that is based on the newly generated neurons (ACSF-LTP). In BAFF Tg-control mice this neurogenesis-dependent LTP was disrupted (WT-control: 126.1±6.1%; BAFF Tg-control: 104.03±7.9%, 60 min after tetanus ($F_{(1,8)}=22.8$, $P=0.0001$). N−3 PUFA-supplemented diet prevented this deficit (BAFF Tg-PUFA: 125.4±6.8%; $F_{(1,8)}=2.7$, $P=0.3$).

These results indicate that n−3 PUFA supplementation restores normal synaptic plasticity in both mature and newly generated neurons in BAFF Tg mice.

Discussion

In this study, we investigated the effects of n−3 PUFA-supplemented diet on hippocampal inflammation, adult neurogenesis and synaptic plasticity impairment in BAFF Tg mice. Our results show that BAFF Tg mice treated with control diet display hippocampal microglia activation, decreased progenitor cell proliferation and DG LTP. N−3 PUFA supplementation prevented these hippocampal abnormalities.

n−3 PUFA supplementation inhibits proinflammatory responses in hippocampus in BAFF Tg mice. Given the epidemiological and clinical data linking n−3 PUFAs deficiency with mood disorders (Parker et al., 2006), autoimmune diseases (Fernandes et al., 2008) and abnormal synaptic plasticity (Lafourcade et al., 2011), it is likely that n−3 PUFA may play a pivotal role in treating autoimmune disease

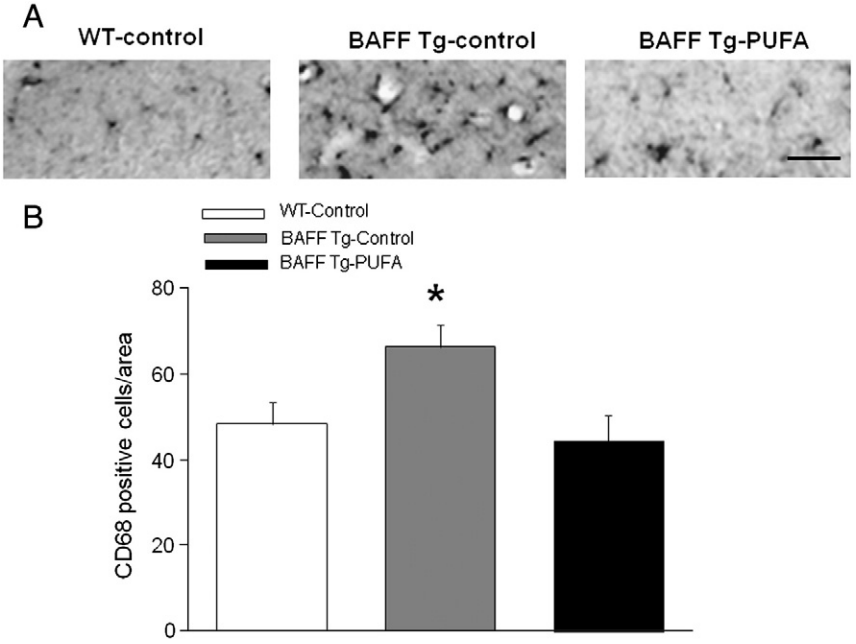

Fig. 1. N−3 PUFA-supplemented diet decreases hippocampal inflammation in BAFF Tg mice. (A) Photomicrographs showing hippocampal immunostaining with CD68. BAFF Tg mice fed with control diet showed increased anti-CD68 positive cells in hippocampus. N−3 PUFA-supplemented diet prevented the development of hippocampal inflammation. Data shown represent the mean±SEM. n=5 for each group. Scale bar=100 μm. *$P<0.05$. New York, USA, 2009.

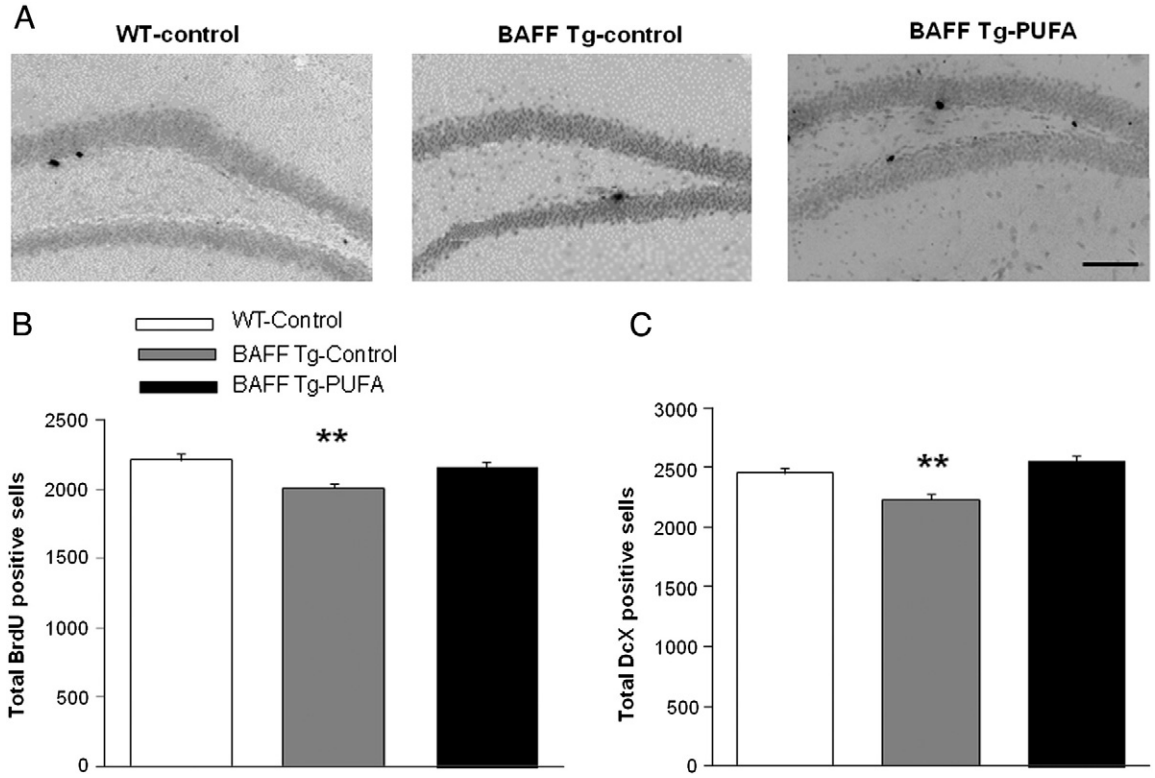

Fig. 2. N−3 PUFA-supplemented diet restores normal hippocampal progenitor cell proliferation in BAFF Tg mice. (A) Representative photomicrographs of $BrdU^+$ labelled cells in dentate gyrus. (B) The number of $BrdU^+$ labelled cells and (C) the total number of DCX^+ cells were significantly increased in BAFF Tg mice fed with N−3 PUFA-supplemented diet. Scale bar 100 μm. The results are mean ± S.E.M, n = 5 each group $^{**}P<0.01$. New York, USA, 2009.

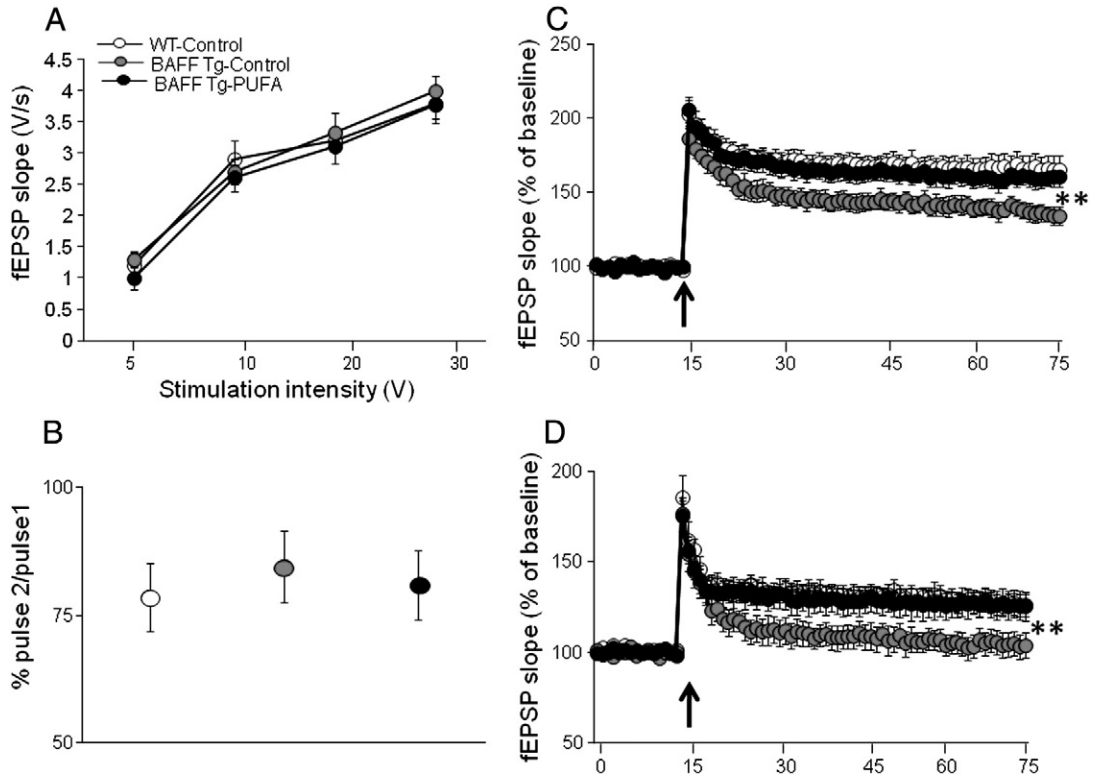

Fig. 3. N−3 PUFA-supplemented diet restores normal dentate gyrus LTP in BAFF Tg mice. (A) BAFF Tg showed similar field input–output relations and paired-pulse depression (B) in the MPP/DG connection compared with age-matched WT ($P>0.05$). BAFF overexpression alters DG LTP. (C) MPP/DG PICRO-LTP in WT and transgenic mice. (D) MPP/DG ACSF-LTP in WT and transgenic mice. Arrow indicates the delivery of the 100 Hz stimulation. N = 5 each group. Error bars represent ± 1 SEM. $^{**}P<0.01$. New York, USA, 2009.

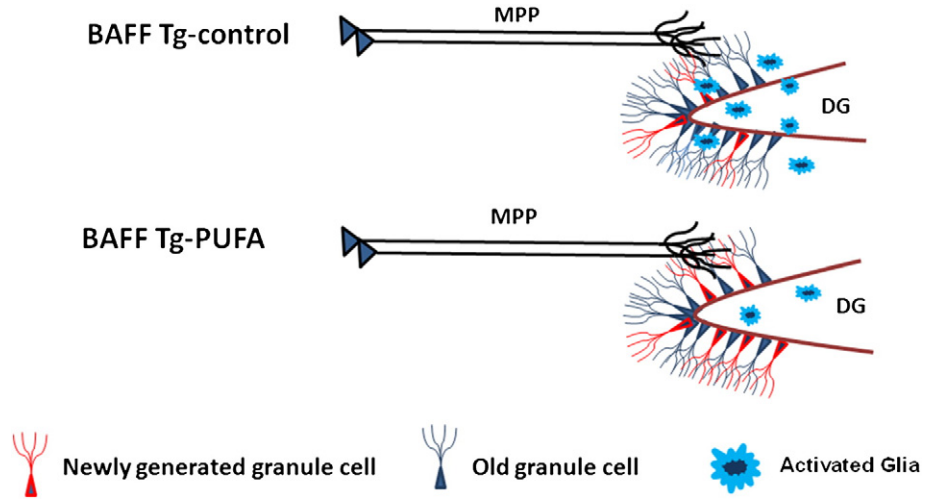

Fig. 4. Schematic representation of the effect of N − 3 PUFA on dentate gyrus plasticity in BAFF Tg mice. Under physiologic condition newly generated granule cells (depicted in red) in the adult hippocampal Dentate Gyrus (DG) became mature neurons (depicted in blue) and functionally integrate into circuits. In BAFF Tg mice inflammation reduced the number of newly generated neuron and decrease synaptic plasticity at the Medial Perforant Pathway (MPP)-DG. N − 3 PUFA-enriched diet reduces DG inflammation and restores normal neurogenesis and neurogenesis-dependent MPP-DG synaptic plasticity. New York, USA, 2009.

and co-morbid mood disorders. Our data confirmed that 6 month old BAFF Tg mice display abnormal hippocampal progenitor cell proliferation (Crupi et al., 2010). n − 3 PUFA supplementation prevented this deficit. Our results are consistent with previous observations that showed beneficial effect of n − 3 PUFA on neurogenesis. For instance, the number of BrdU-positive dividing cells is significantly higher in the hippocampus of fat-1 transgenic mice compared to WT littermates (He et al., 2009). The fat-1 mouse is a transgenic model rich in endogenous n − 3 fatty acids; furthermore, similar results have also been reported with dietary supplementation (Kawakita et al., 2006) (Beltz et al., 2007) (Venna et al., 2009). The mechanisms by which n − 3 PUFA exert modulatory effect on DG neurogenesis need to be identified. It is likely that n − 3 PUFA may influence neurogenesis through multiple mechanisms. In particular, it has been shown that n − 3 PUFA regulates neural stem cell proliferation and differentiation (Wada et al., 2006) through increased expression level of basic helix-loop-helix (bHLH) transcription factors promoting cell cycle exit (Katakura et al., 2009). In addition, n − 3 PUFA-enriched diet promotes hippocampal plasticity and over-expression of both synaptophysin and Brain-Derived Neurotrophic Factor (BDNF) (Venna et al., 2009). Several lines of evidence support the involvement of BDNF in preventing neurogenesis abnormalities in BAFF Tg mice given that this trophic factor has been associated with increased proliferation of newborn neurons in the adult hippocampus (Li et al., 2008) and modulation of hippocampal morphological and functional plasticity (Alonso et al., 2004). Neuroinflammation exerts well-known detrimental effects on new neurons morphology and electrophysiology (Monje et al., 2003) (Wood et al., 2011). It is thus conceivable that the beneficial effect of n − 3 PUFA on neurogenesis in BAFF Tg mice may be due to anti-inflammatory effects (Bazan, 2006) (Marcheselli et al., 2003). Inflammatory blockade induces a broad spectrum of effects that could modulate neurogenesis in several ways. The decrease in proinflammatory cytokines and attenuation of HPA axis activity and serum glucocorticoid levels (Gould et al., 1997) (Delarue et al., 2006) (Navarro et al., 2011) may contribute to restore normal progenitor cell proliferation.

Our data showed that n − 3 PUFA dietary supplementation prevented decrease in DG neurogenesis-dependent and neurogenesis-independent LTP in BAFF Tg mice. These results are consisted with previous reports that showed a positive effect of n − 3 PUFA on age-related decrease in LTP in rodents (McGahon et al. (1997, 1999a, b) (Kotani et al., 2003) (Kashiyae et al., 2009). Neurogenesis-dependent LTP occurs at the MPP/DG synapses and depends on young adult-born neurons (Saxe et al., 2006). Our data indicate that, as previously reported, increasing the number of adult-born neurons is sufficient to enhance this form of LTP (Saxe et al., 2006) (Wang et al., 2008) (Sahay et al., 2011). Our PUFA treatment reversed also the impairment of MPP/DG LTP recorded in the presence of picrotoxin. This form of LTP depends upon mature granule neurons synaptic activity (Saxe et al., 2006). The modulation of PICRO-LTP might be due to the blockage of hippocampal microglia activation as previously reported in different animal models (Calon et al., 2005) (Green et al., 2007) (Fig. 4). Furthermore, n − 3 PUFA supplementation might regulate PICRO-LTP through effects on membrane fluidity, receptor binding proteins, AMPA receptor activation (McGahon et al., 1999a) (Lu et al., 2001) (Martin et al., 2002) and on calcium homeostasis (Kashiyae et al., 2009).

Conclusions

Overall, the results from the present study suggest that n − 3 PUFA-supplemented diet prevents age-dependent deficit in hippocampal plasticity in BAFF Tg mice. Future studies are needed to identify the mechanisms regulating these effects and to probe whether these plastic changes contribute to behaviors.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Acknowledgment

We thank Linda Spatz for providing transgenic animals and for helpful discussions during manuscript preparation.

References

Alonso, M., Medina, J.H., Pozzo-Miller, L., 2004. ERK1/2 activation is necessary for BDNF to increase dendritic spine density in hippocampal CA1 pyramidal neurons. Learn. Mem. 11, 172–178.

Bazan, N.G., 2006. Cell survival matters: docosahexaenoic acid signaling, neuroprotection and photoreceptors. Trends Neurosci. 29, 263–271.

Beltz, B.S., Tlusty, M.F., Benton, J.L., Sandeman, D.C., 2007. Omega-3 fatty acids upregulate adult neurogenesis. Neurosci. Lett. 415, 154–158.

Bhattacharya, A., Lawrence, R.A., Krishnan, A., Zaman, K., Sun, D., Fernandes, G., 2003. Effect of dietary n − 3 and n − 6 oils with and without food restriction on activity of antioxidant enzymes and lipid peroxidation in livers of cyclophosphamide treated autoimmune-prone NZB/W female mice. J. Am. Coll. Nutr. 22, 388–399.

Bianchi, M., Sacerdote, P., Panerai, A.E., 1994. Fluoxetine reduces inflammatory edema in the rat: involvement of the pituitary-adrenal axis. Eur. J. Pharmacol. 263, 81–84.
Calon, F., Lim, G.P., Morihara, T., et al., 2005. Dietary n−3 polyunsaturated fatty acid depletion activates caspases and decreases NMDA receptors in the brain of a transgenic mouse model of Alzheimer's disease. Eur. J. Neurosci. 22, 617–626.
Cermak, J.M., Papas, A.S., Sullivan, R.M., Dana, M.R., Sullivan, D.A., 2003. Nutrient intake in women with primary and secondary Sjogren's syndrome. Eur. J. Clin. Nutr. 57, 328–334.
Chung, Y.C., Kim, S.R., Park, J.Y., et al., 2011. Fluoxetine prevents MPTP-induced loss of dopaminergic neurons by inhibiting microglial activation. Neuropharmacology 60, 963–974.
Croker, J.A., Kimberly, R.P., 2005. SLE: challenges and candidates in human disease. Trends Immunol. 26, 580–586.
Crupi, R., Cambiaghi, M., Spatz, L., et al., 2010. Reduced adult neurogenesis and altered emotional behaviors in autoimmune-prone B-cell activating factor transgenic mice. Biol. Psychiatry 67, 558–566.
Delarue, J., Li, C.H., Cohen, R., Corporeau, C., Simon, B., 2006. Interaction of fish oil and a glucocorticoid on metabolic responses to an oral glucose load in healthy human subjects. Br. J. Nutr. 95, 267–272.
Fernandes, G., Bhattacharya, A., Rahman, M., Zaman, K., Banu, J., 2008. Effects of n−3 fatty acids on autoimmunity and osteoporosis. Front. Biosci. 13, 4015–4020.
Gould, E., McEwen, B.S., Tanapat, P., Galea, L.A., Fuchs, E., 1997. Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. J. Neurosci. 17, 2492–2498.
Green, K.N., Martinez-Coria, H., Khashwji, H., et al., 2007. Dietary docosahexaenoic acid and docosapentaenoic acid ameliorate amyloid-beta and tau pathology via a mechanism involving presenilin 1 levels. J. Neurosci. 27, 4385–4395.
Grider, M.H., Chen, Q., Shine, H.D., 2006. Semi-automated quantification of axonal densities in labeled CNS tissue. J. Neurosci. Methods 155, 172–179.
Groom, J., Kalled, S.L., Cutler, A.H., et al., 2002. Association of BAFF/BLyS overexpression and altered B cell differentiation with Sjogren's syndrome. J. Clin. Invest. 109, 59–68.
He, C., Qu, X., Cui, L., Wang, J., Kang, J.X., 2009. Improved spatial learning performance of fat-1 mice is associated with enhanced neurogenesis and neuritogenesis by docosahexaenoic acid. Proc. Natl. Acad. Sci. U. S. A. 106, 11370–11375.
Kashiyae, Y., Kontani, M., Kawashima, H., Kiso, Y., Kudo, Y., Sakakibara, M., 2009. Arachidonic acid enhances intracellular calcium levels in dentate gyrus, but not CA1, in aged rat. Neurosci. Res. 64, 143–151.
Katakura, M., Hashimoto, M., Shahdat, H.M., et al., 2009. Docosahexaenoic acid promotes neuronal differentiation by regulating basic helix-loop-helix transcription factors and cell cycle in neural stem cells. Neuroscience 160, 651–660.
Kawakita, E., Hashimoto, M., Shido, O., 2006. Docosahexaenoic acid promotes neurogenesis in vitro and in vivo. Neuroscience 139, 991–997.
Kotani, S., Nakazawa, H., Tokimasa, T., et al., 2003. Synaptic plasticity preserved with arachidonic acid diet in aged rats. Neurosci. Res. 46, 453–461.
Krishnan, V., Nestler, E.J., 2010. Linking molecules to mood: new insight into the biology of depression. Am. J. Psychiatry 167, 1305–1320.
Lafourcade, M., Larrieu, T., Mato, S., et al., 2011. Nutritional omega-3 deficiency abolishes endocannabinoid-mediated neuronal functions. Nat. Neurosci. 14, 345–350.
Lefkowith, J.B., Klahr, S., 1996. Polyunsaturated fatty acids and renal disease. Proc. Soc. Exp. Biol. Med. 213, 13–23.
Li, Y., Luikart, B.W., Birnbaum, S., et al., 2008. TrkB regulates hippocampal neurogenesis and governs sensitivity to antidepressive treatment. Neuron 59, 399–412.
Lu, W., Man, H., Ju, W., Trimble, W.S., MacDonald, J.F., Wang, Y.T., 2001. Activation of synaptic NMDA receptors induces membrane insertion of new AMPA receptors and LTP in cultured hippocampal neurons. Neuron 29, 243–254.
Ma, D., Lu, L., Boneva, N.B., et al., 2008. Expression of free fatty acid receptor GPR40 in the neurogenic niche of adult monkey hippocampus. Hippocampus 18, 326–333.
Ma, D., Zhang, M., Larsen, C.P., et al., 2010. DHA promotes the neuronal differentiation of rat neural stem cells transfected with GPR40 gene. Brain Res. 1330, 1–8.
Mackay, F., Schneider, P., 2009. Cracking the BAFF code. Nat. Rev. Immunol. 9, 491–502.
Mackay, F., Woodcock, S.A., Lawton, P., et al., 1999. Mice transgenic for BAFF develop lymphocytic disorders along with autoimmune manifestations. J. Exp. Med. 190, 1697–1710.
Mackay, G.M., Forrest, C.M., Christofides, J., et al., 2009. Kynurenine metabolites and inflammation markers in depressed patients treated with fluoxetine or counselling. Clin. Exp. Pharmacol. Physiol. 36, 425–435.
Malberg, J.E., Eisch, A.J., Nestler, E.J., Duman, R.S., 2000. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J. Neurosci. 20, 9104–9110.
Marcheselli, V.L., Hong, S., Lukiw, W.J., et al., 2003. Novel docosanoids inhibit brain ischemia-reperfusion-mediated leukocyte infiltration and pro-inflammatory gene expression. J. Biol. Chem. 278, 43807–43817.
Martin, D.S., Spencer, P., Horrobin, D.F., Lynch, M.A., 2002. Long-term potentiation in aged rats is restored when the age-related decrease in polyunsaturated fatty acid concentration is reversed. Prostaglandins Leukot. Essent. Fatty Acids 67, 121–130.
McGahon, B., Clements, M.P., Lynch, M.A., 1997. The ability of aged rats to sustain long-term potentiation is restored when the age-related decrease in membrane arachidonic acid concentration is reversed. Neuroscience 81, 9–16.
McGahon, B.M., Martin, D.S., Horrobin, D.F., Lynch, M.A., 1999a. Age-related changes in LTP and antioxidant defenses are reversed by an alpha-lipoic acid-enriched diet. Neurobiol. Aging 20, 655–664.
McGahon, B.M., Martin, D.S., Horrobin, D.F., Lynch, M.A., 1999b. Age-related changes in synaptic function: analysis of the effect of dietary supplementation with omega-3 fatty acids. Neuroscience 94, 305–314.
Melchers, F., 2003. Actions of BAFF in B cell maturation and its effects on the development of autoimmune disease. Ann. Rheum. Dis. 62 (Suppl. 2), ii25–ii27.
Monje, M.L., Toda, H., Palmer, T.D., 2003. Inflammatory blockade restores adult hippocampal neurogenesis. Science 302, 1760–1765.
Navarro, C., Gonzalez-Alvarez, I., Gonzalez-Alvarez, M., et al., 2011. Influence of polyunsaturated fatty acids on Cortisol transport through MDCK and MDCK-MDR1 cells as blood-brain barrier in vitro model. Eur. J. Pharm. Sci. 42, 290–299.
Osumi, N., 2010. Fatty acid signal, neurogenesis, and psychiatric disorders. Nihon Shinkei Seishin Yakurigaku Zasshi 30, 141–148.
Parker, G., Gibson, N.A., Brotchie, H., Heruc, G., Rees, A.M., Hadzi-Pavlovic, D., 2006. Omega-3 fatty acids and mood disorders. Am. J. Psychiatry 163, 969–978.
Pestka, J.J., 2010. n−3 polyunsaturated fatty acids and autoimmune-mediated glomerulonephritis. Prostaglandins Leukot. Essent. Fatty Acids 82, 251–258.
Robson, L.G., Dyall, S., Sidloff, D., Michael-Titus, A.T., 2008. Omega-3 polyunsaturated fatty acids increase the neurite outgrowth of rat sensory neurones throughout development and in aged animals. Neurobiol. Aging 31, 678–687.
Sahay, A., Scobie, K.N., Hill, A.S., O'Carroll, C.M., Kheirbek, M.A., Burghardt, N.S., Fenton, A.A., Dranovsky, A., Hen, R., 2011. Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. Nature 472 (7344), 466–470.
Saxe, M.D., Battaglia, F., Wang, J.W., et al., 2006. Ablation of hippocampal neurogenesis impairs contextual fear conditioning and synaptic plasticity in the dentate gyrus. Proc. Natl. Acad. Sci. U. S. A. 103, 17501–17506.
Simopoulos, A.P., 2002. Omega-3 fatty acids in inflammation and autoimmune diseases. J. Am. Coll. Nutr. 21, 495–505.
Venna, V.R., Deplanque, D., Allet, C., Belarbi, K., Hamdane, M., Bordet, R., 2009. PUFA induce antidepressant-like effects in parallel to structural and molecular changes in the hippocampus. Psychoneuroendocrinology 34, 199–211.
Wada, K., Nakajima, A., Katayama, K., et al., 2006. Peroxisome proliferator-activated receptor gamma-mediated regulation of neural stem cell proliferation and differentiation. J. Biol. Chem. 281, 12673–12681.
Wang, J.W., David, D.J., Monckton, J.E., Battaglia, F., Hen, R., 2008. Chronic fluoxetine stimulates maturation and synaptic plasticity of adult-born hippocampal granule cells. J. Neurosci. 28, 1374–1384.
Wood, J.C., Jackson, J.S., Jakubs, K., Chapman, K.Z., Ekdahl, C.T., Kokaia, Z., Kokaia, M., Lindvall, O., 2011. Functional integration of new hippocampal neurons following insults to the adult brain is determined by characteristics of pathological environment. Exp. Neurol. 229 (2), 484–493.
Yamashima, T., 2008. A putative link of PUFA, GPR40 and adult-born hippocampal neurons for memory. Prog. Neurobiol. 84, 105–115.