



Regular Article

Dietary curcumin counteracts the outcome of traumatic brain injury on oxidative stress, synaptic plasticity, and cognition

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Abstract

The pervasive action of oxidative stress on neuronal function and plasticity after traumatic brain injury (TBI) is becoming increasingly recognized. Here, we evaluated the capacity of the powerful antioxidant curry spice curcumin ingested in the diet to counteract the oxidative damage encountered in the injured brain. In addition, we have examined the possibility that dietary curcumin may favor the injured brain by interacting with molecular mechanisms that maintain synaptic plasticity and cognition. The analysis was focused on the BDNF system based on its action on synaptic plasticity and cognition by modulating synapsin I and CREB. Rats were exposed to a regular diet or a diet high in saturated fat, with or without 500 ppm curcumin for 4 weeks ($n = 8/\text{group}$), before a mild fluid percussion injury (FPI) was performed. The high-fat diet has been shown to exacerbate the effects of TBI on synaptic plasticity and cognitive function. Supplementation of curcumin in the diet dramatically reduced oxidative damage and normalized levels of BDNF, synapsin I, and CREB that had been altered after TBI. Furthermore, curcumin supplementation counteracted the cognitive impairment caused by TBI. These results are in agreement with previous evidence, showing that oxidative stress can affect the injured brain by acting through the BDNF system to affect synaptic plasticity and cognition. The fact that oxidative stress is an intrinsic component of the neurological sequel of TBI and other insults indicates that dietary antioxidant therapy is a realistic approach to promote protective mechanisms in the injured brain.

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Introduction

Traumatic brain injury (TBI) is a devastating condition that has long-term consequences on the cognitive ability of individuals. The results of new studies indicate that impaired cognition after TBI appears to be associated with dysfunction in molecular systems that support synaptic plasticity such as brain-derived neurotrophic factor (BDNF) (Wu et al., 2003). Oxidative stress is one of the hallmarks of TBI that has the potential to initiate the events resulting in protracted neuronal function and plasticity. We have previously shown that increased free radical formation associated with the consumption of a diet high in saturated fat worsened the outcome of TBI on cognition and neuroplasticity (Wu et al., 2003, 2004a). The

results of these studies seem to indicate that oxidative stress and synaptic plasticity are interrelated events and that the study of the mechanisms involved in this interface can open new avenues to better understand the TBI pathology. In the present study, we evaluated the action of a powerful antioxidant on the BDNF system and its downstream synaptic plasticity effectors synapsin I and cyclic AMP-response element-binding protein (CREB). We have studied the effects of curcumin supplemented in the diet given that dietary manipulation is a realistic approach to intervene the brain.

The phenolic yellow curry pigment curcumin has potent anti-inflammatory and antioxidant activities that can function to reduce oxidative damage and cognitive deficits associated with aging. In particular, curcumin has been shown to reduce oxidative damage and amyloid pathology in Alzheimer's disease (Frautschy et al., 2001; Lim et al., 2001; Ono et al., 2004; Thiyagarajan and Sharma, 2004). The potency of curcumin in its ability to protect the brain from free radical-

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induced damage is thought to be several times stronger than that of vitamin E (Martin-Aragon et al., 1997). Based on the above mentioned considerations, we performed this study to evaluate the protective action of curcumin against the adverse effects of TBI on cognition and neuroplasticity. We also evaluated the effects of curcumin after the consumption of a diet high in saturated fat since the latter aggravates the outcome of TBI (Wu et al., 2003).

Compromised BDNF function in the injured brain can weaken the molecular substrates for maintaining normal neuronal function. BDNF facilitates synaptic transmission (Kang and Schuman, 1996; Levine et al., 1998; Sherwood and Lo, 1999; Tyler and Pozzo-Miller, 2001) and promotes neuronal excitability (Bolton et al., 2000; Kafitz et al., 1999), such that its action appears to be crucial for maintaining molecular processes underlying cognitive function such as long-term potentiation (Korte et al., 1995; Linnarsson et al., 1997; Patterson et al., 1996). BDNF promotes the synthesis (Wang et al., 1995) and phosphorylation (Jovanovic et al., 1996) of synapsin I, which 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). CREB, a transcription factor involved in learning and memory, is an important modulator of gene expression induced by BDNF (Finkbeiner, 2000).

Materials and methods

Experimental design and tissue preparation

Male Sprague–Dawley rats (Charles River Laboratories, Inc., Wilmington, MA) approximately 2 months old 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, one set of rats was randomly assigned to regular diet or a saturated high-fat diet with or without curcumin (500 ppm) for 4 weeks. This dose of curcumin has been shown to prevent cognitive deficit in animal models of Alzheimer's disease (Frautschy et al., 2001). The regular diet is low in saturated fat (13% of energy from fat) and contains complex carbohydrate (starch, 59% energy). The high-fat diet is high in saturated and monounsaturated (primarily from lard plus a small amount of corn oil, ~39% energy) and high in refined sugar (sucrose, ~40% energy). The diets, fed ad libitum, were provided in powder (TestDiet Inc., Richmond, IN) in large bowl and contained a standard vitamin and mineral mix with all essential nutrients. After 4 weeks on the various diets, a mild fluid percussion injury (FPI) was performed in approximately half of the rats. After 1 week of being maintained on the same diet post-injury, rats ($n = 8$ per group) were killed by decapitation, and the brain was rapidly dissected, frozen on dry ice, and stored at -70°C until use for biochemical analyses. By the end of the experiment, there were 7 experimental groups: i) regular diet plus sham, ii) regular diet plus FPI; iii) high-fat diet plus sham; iv) high-fat diet plus FPI; v) regular diet plus

curcumin plus sham; and vi) regular diet plus curcumin plus FPI; vii) high-fat diet plus curcumin plus FPI. A high-fat curcumin plus sham group was excluded from the design since 4 weeks of high-fat treatment has shown no effects on sham animals (Wu et al., 2003). The body weight was recorded every week. The body weight at the beginning of diet experiment was: regular diet (272 ± 5 g), high-fat diet (275 ± 9 g), regular diet plus curcumin (286 ± 15 g), and high-fat diet plus curcumin (289 ± 8 g). The body weight at 4 week after maintaining on diet was: regular diet (425 ± 11 g), high-fat diet (432 ± 7 g), regular diet plus curcumin (435 ± 16 g), and high-fat diet plus curcumin (439 ± 12 g). The food intake was recorded every other day. The average food intake per day during the fourth week on diet was: regular diet (34.6 ± 4.1 g), high-fat diet (30.5 ± 3.2 g), regular diet plus curcumin (33.1 ± 3.1 g), and high-fat diet plus curcumin (31.1 ± 2.5 g). There was no group difference in all groups on body weight and food intake between sham and FPI conditions at the end of experiment. 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, 2004b). 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 hippocampus 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. Because of the large number of samples (56, 7 groups with 8 animals per group), we run separate gels with the same experimental controls included in each gel. Experimental values were standardized according to the internal control values. The entire band was integrated in each group and analyzed using NIH image software.

Cognitive testing

The cognitive testing was performed in a water maze as described previously (Molteni et al., 2002, 2004; Wu et al., 2003, 2004a,b). Briefly, the rats ($n = 8$ in each group) 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 equally spaced start locations that were randomly changed every trial. Each trial lasted until the rat found the platform or for a maximum 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 escape latencies to find the platform were recorded. In order to assess spatial memory retention, spatial probe tests were performed at 4 h after the last try by removing the platform from the pool. The rats were allowed to swim for 1 min in the pool without the escape platform, and the percentage of time spent in each zone was calculated.

ELISA

Hippocampal tissue ipsilateral to FPI 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 g/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 Micro BCA 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, phospho-synapsin I (p-synapsin I), CREB, and phospho-CREB (p-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, and anti-p-synapsin I (1:2000, Santa Cruz Biotechnology, Santa Cruz, CA) followed by anti-goat IgG horseradish peroxidase conjugate (Santa Cruz Biotechnology); anti-CREB, anti-p-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.

Statistical analysis

Actin was employed as internal standard for Western blot. The regular diet-fed 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 group as presented in bar figures and represented the mean \pm 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

Effect of curcumin on oxidative stress in TBI animals

Oxidative damage was assessed by using Western blot analysis of DNPH-derivatized carbonyl groups on oxidized proteins. The samples for measurement of oxidized protein were from hippocampus in each group. Representative examples of Oxyblot are shown in Fig. 1A. The oxidized protein levels were significantly increased in TBI animals fed regular diet (139%) or high-fat diet (239%) relative to sham rats (Fig. 1B). TBI animals fed regular diet or high-fat diet containing curcumin, however, had a significant lower level of oxidized proteins (45% and 47% respectively) compared with sham animals fed regular diet (Fig. 1B). High fat did not produce significant effects on oxidized protein levels in sham rats (data not shown). In addition, curcumin supplementation did not affect oxidized protein levels in sham rats (Fig. 1C). The sham group fed regular diet was used as a control to normalize other bands from different groups. After statistical analysis, the Oxyblot data were converted to percent of sham control (Sham-regular diet) group ($100 \pm 6\%$) as presented in bar figures and represented the mean \pm SEM (%).

Effects of curcumin on BDNF and its downstream effectors synapsin I and CREB in TBI animals

Our previous study revealed a significant decrease of BDNF in TBI animals with more pronounced effect in high-fat diet-fed rats relative to regular diet-fed animals (Wu et al., 2003). In

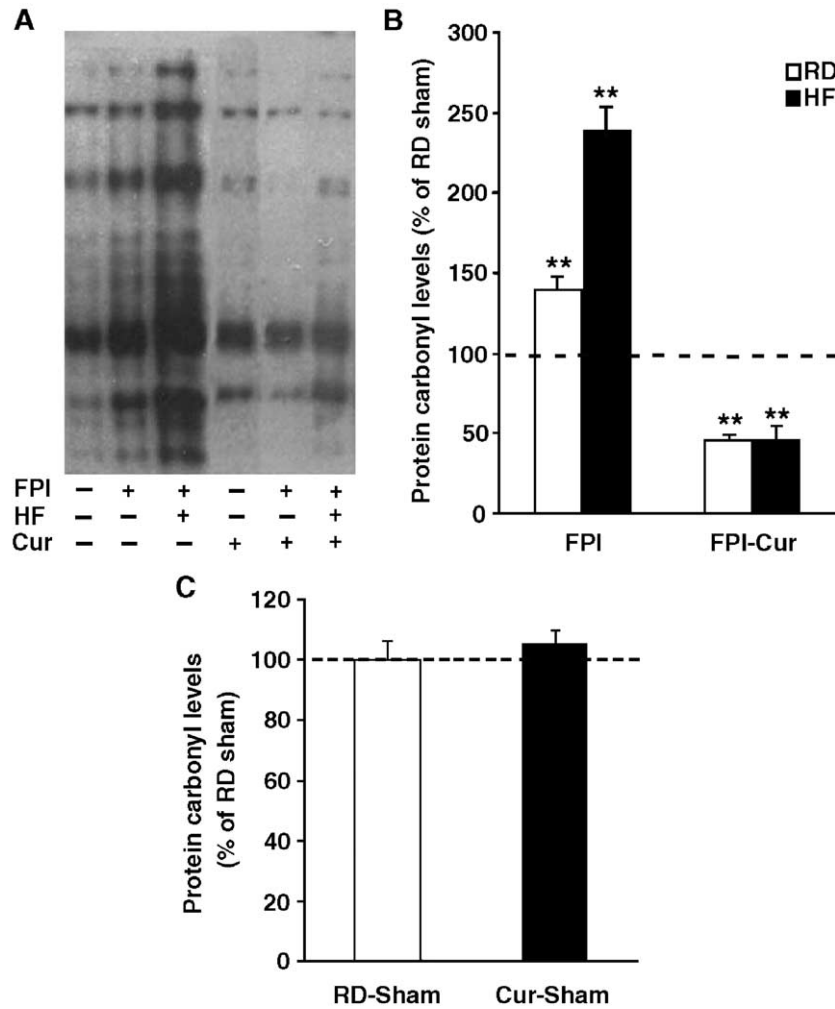


Fig. 1. Levels of oxidized protein in the hippocampus determined by Oxyblot kit. (A) Representative gel bands of Oxyblot from hippocampal tissue in each animal group. (B) Effects of curcumin on oxidized protein levels. FPI increased oxidized protein levels, but these effects were counteracted by dietary supplementation of curcumin. High fat did not produce significant effects on oxidized protein levels in sham rats (data not shown). (C) Curcumin supplementation did not affect oxidized protein levels in sham rats. The values were converted to percent of RD sham (mean \pm SEM). The number of rats was 8 within each group. ** $P < 0.01$. ANOVA, Fisher's test. RD, regular diet; HF, high fat; FPI, fluid percussion injury; Cur, curcumin.

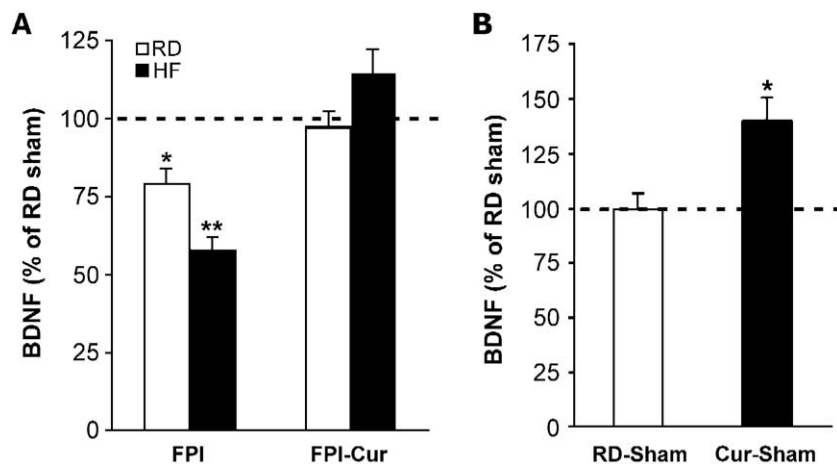


Fig. 2. Effects of curcumin supplementation on BDNF levels in the hippocampus of FPI rats determined by ELISA. (A) Curcumin reversed the BDNF reduction in FPI rats. High fat did not significantly affect BDNF in sham rats (data not shown). (B) Curcumin increased BDNF levels in sham rats. The values were converted to percent of RD sham (mean \pm SEM). The number of rats was 8 within each group. * $P < 0.05$; ** $P < 0.01$. ANOVA, Fisher's test. RD, regular diet; HF, high fat; FPI, fluid percussion injury; Cur, curcumin.

the current study, supplementation of curcumin in the diet normalized BDNF levels in the hippocampus of TBI rats fed regular diet or high-fat diet (97% in TBI rats fed regular diet containing curcumin; 114% in TBI animals fed high-fat diet containing curcumin; Fig. 2A). High fat did not significantly affect BDNF in sham rats (data not shown). In addition, curcumin supplementation increased BDNF levels (140%) in sham rats (Fig. 2B).

BDNF facilitates synaptic transmission and regulates gene expression through activation of synapsin I and CREB (Jovanovic et al., 1996; Finkbeiner, 2000; 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 investigate whether curcumin supplemented in the diet can protect against disrupted synaptic plasticity after TBI, we measured the protein

expression of synapsin I and phosphorylated-synapsin I (p-synapsin I) in the hippocampus by Western blot analysis. The results showed that TBI reduced synapsin I in rats fed regular diet or high-fat diet (82% and 69% respectively; Fig. 3A), whereas curcumin reversed these effects (90% and 93% respectively) relative to sham animals. TBI has no effects on p-synapsin I under regular diet conditions (Wu et al., 2003). TBI plus high-fat diet consumption led to reduction of p-synapsin I (65%), but this reduction was prevented by curcumin (120%) relative to sham rats (Fig. 3B). High fat did not produce significant effects on synapsin I and p-synapsin I levels in sham rats (data not shown). In addition, curcumin supplementation did not affect levels of synapsin I (102%) and p-synapsin I (109%) in sham rats (Figs. 3C and D).

We also measured the protein expression of CREB and phosphorylated-CREB (p-CREB) in the hippocampus by

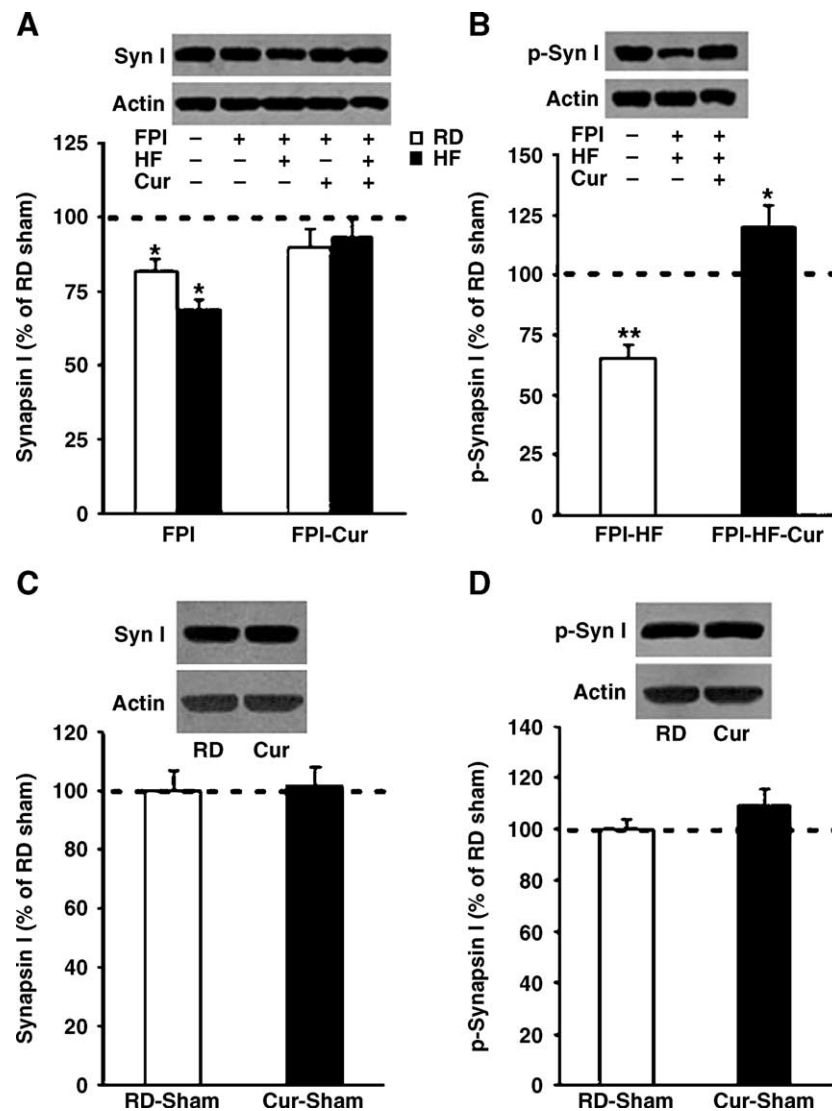


Fig. 3. Effects of curcumin supplementation on the levels of synapsin I and p-synapsin I in FPI rats. (A) FPI reduced synapsin I, and these effects were counteracted by curcumin. (B) FPI plus HF-reduced p-synapsin I was reversed by curcumin. High fat did not produce significant effects on synapsin I and p-synapsin I levels in sham rats (data not shown). Curcumin did not affect levels of synapsin I (C) and p-synapsin I (D) in sham rats. The levels of synapsin I and p-synapsin I were measured by Western blot analysis using actin as standard control. The values were converted to percent of RD sham (mean \pm SEM). The number of rats was 8 within each group. * $P < 0.05$; ** $P < 0.01$. ANOVA, Fisher's test. RD, regular diet; HF, high fat; FPI, fluid percussion injury; Cur, curcumin.

Western blot analysis. The results showed that TBI reduced CREB in rats fed regular diet or high-fat diet (80% and 65% respectively; Fig. 4A), whereas curcumin reversed these effects (92% and 90% respectively) relative to sham animals. TBI has no effects on p-CREB under regular diet conditions (Wu et al., 2003). TBI plus high-fat diet consumption led to reduction of p-CREB (60%), but this reduction was reversed by curcumin (89%) relative to sham rats (Fig. 4B). High fat did not produce significant effects on CREB and p-CREB levels in sham rats (data not shown). In addition, curcumin supplementation did not affect levels of CREB (105%) and p-CREB (93%) in sham rats (Figs. 4C and D).

Effect of curcumin on the cognitive function in TBI animals

Our previous study revealed that ingesting high-fat diet aggravated the effects of TBI on impaired cognitive function

(Wu et al., 2003). To determine whether supplementation of curcumin in the diet can provide protection from cognitive impairment following TBI, we maintained some rats on regular diet or high-fat diet containing 500 ppm curcumin. The learning performance and memory retention were detected in a Morris water maze. The results demonstrated that TBI rats perform worse, showing longer escape latencies to locate the platform in Morris water maze than the sham rats ($P < 0.05$; Fig. 5A). Furthermore, consumption of high-fat diet worsened their performance by increasing their escape latencies ($P < 0.05$; Fig. 5A). Supplementation of curcumin, however, counteracted the effects of TBI (Fig. 5A). Furthermore, TBI rats with previous exposure to the high-fat diet showed less swimming time in the target zone relative to sham animals ($P < 0.05$), whereas curcumin reversed these effects (Fig. 5B). High fat did not significantly affect water maze performance in sham rats (data not shown). In addition,

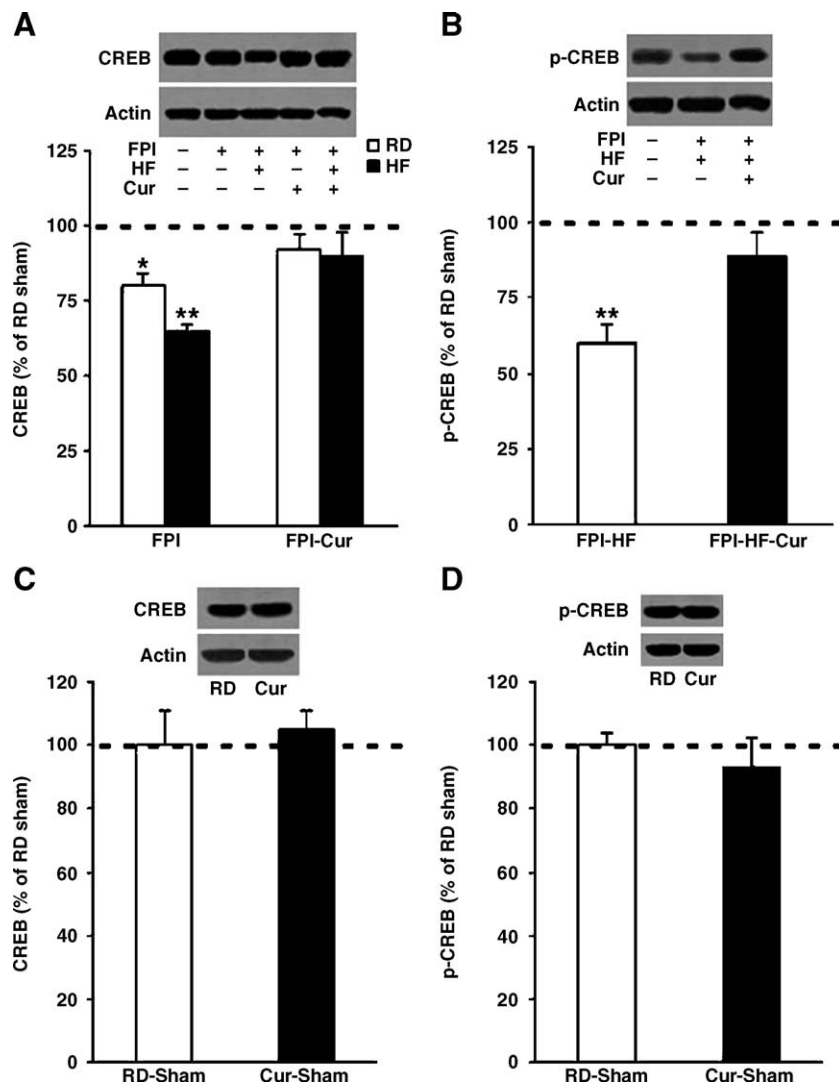


Fig. 4. Effects of curcumin supplementation on the levels of CREB and p-CREB in FPI animals. (A) FPI led to reduction of CREB, whereas curcumin counteracted these effects. (B) The reductions in p-CREB caused by FPI plus HF were reversed by curcumin. High fat did not produce significant effects on CREB and p-CREB levels in sham rats (data not shown). Curcumin did not affect levels of CREB (C) and p-CREB (D) in sham rats. The levels of CREB and p-CREB were measured by Western blot analysis using actin as standard control. The values were converted to percent of sham (mean \pm SEM). The number of rats was 8 within each group. * $P < 0.05$; ** $P < 0.01$. ANOVA, Fisher's test. RD, regular diet; HF, high fat; FPI, fluid percussion injury; Cur, curcumin.

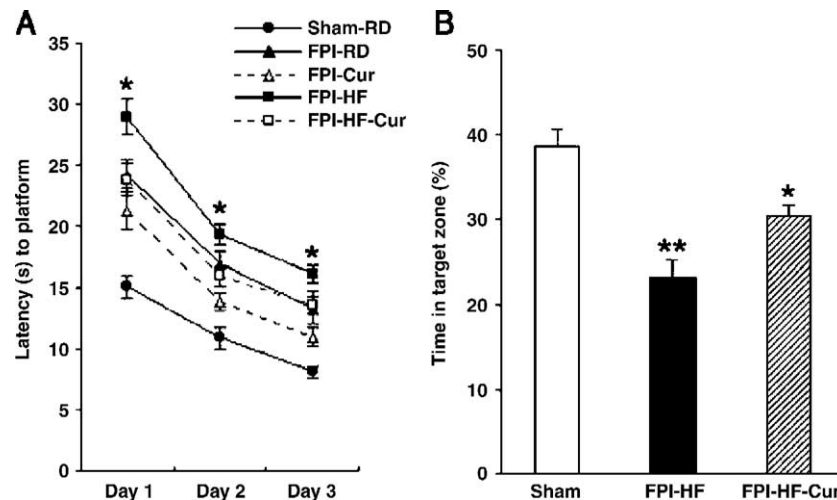


Fig. 5. Curcumin supplementation provides protection against cognitive disability in FPI rats. (A) Learning performance was scored as average of escape latencies to locate the platform in the Morris water maze. The escape latencies were longer in FPI rats compared to sham animals. FPI plus HF intervened rats showed the longest latencies. Curcumin counteracted the learning disability in FPI rats. (B) Spatial probe tests were performed by removing the platform from the pool. The rats were allowed to swim for 1 min in the pool without the escape platform, and the percentage of time spent in each zone was calculated. FPI plus HF led to impaired memory retention, but this impairment was reversed by curcumin. High fat did not significantly affect water maze performance in sham rats (data not shown). In addition, curcumin did not significantly affect performance in the water maze in sham rats (data not shown). The number of rats was 8 within each group. RD, regular diet; HF, high fat; FPI, fluid percussion injury; Cur, curcumin.

there is no significant difference in swimming speed in all groups, consistent with our previous observations (Wu et al., 2004b). Curcumin did not significantly affect performance in the water maze in sham rats (data not shown).

Discussion

The results show that TBI increases oxidative damage and impairs cognitive function and that these events may be related to a disruption in molecular systems associated with the action of BDNF. We provide evidence that the dietary application of the antioxidant curcumin can reduce the deleterious effects of TBI on synaptic plasticity and cognition. These results are consistent with the notion that oxidative stress plays a major role on the cognitive dysfunction associated with TBI. An added interesting aspect of these studies is the demonstrated capacity of dietary factors to modulate plasticity and function of the brain after insult.

TBI and oxidative stress

We detected markedly elevated protein carbonyl formation in TBI animals using a modified Western blot analysis of DNPH-derivatized carbonyls, which is consistent with the notion that oxidative stress is a prevalent condition in the traumatically injured brain (Wu et al., 2004b) and Alzheimer's disease (Lim et al., 2001). Carbonyls levels are considered indicative of protein oxidation associated with free radical formation (Frautschy et al., 2001; Lim et al., 2001; Ono et al., 2004; Thiyagarajan and Sharma, 2004). Accumulation of free radicals is associated with cognitive deficits in aging (Fukui et al., 2002; Joseph et al., 1998; Liu et al., 2003; Nagai et al., 2003; Sung et al., 2004; Veinbergs et al., 2000) and has been observed in TBI (Marklund et al.,

2001; Paolin et al., 2002). As discussed below, it is possible that oxidative damage may reduce BDNF-related synaptic plasticity and cognitive abilities. The present findings suggest that curcumin may help to counteract the oxidative damage with subsequent effects on the action of BDNF on synaptic plasticity after TBI (Fig. 6).

Supplementation of curcumin in the diet dramatically reduced the elevated protein carbonyl levels after injury. Curcumin is a potent free radicals scavenger and has been shown to reduce oxidative damage and Alzheimer pathology (Frautschy et al., 2001; Lim et al., 2001; Ono et al., 2004; Thiyagarajan and Sharma, 2004). The antioxidant activity of curcumin may be due to the presence in its structure of two electrophilic α , β -unsaturated carbonyl groups, which can react

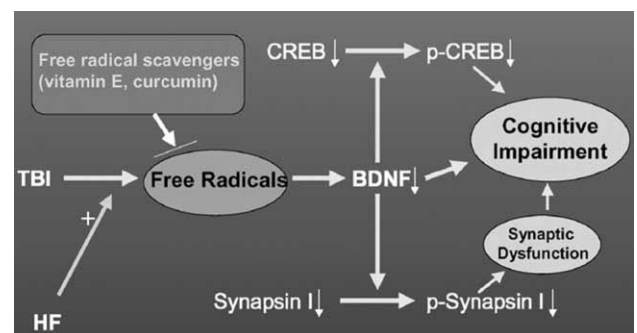


Fig. 6. Possible mechanisms underlying the effects of antioxidant factors (i.e. vitamin E and curcumin) on cognition and synaptic plasticity after TBI. TBI elevates production of free radicals, which in turn may reduce levels and function of BDNF and its synaptic plasticity effectors synapsin I and CREB. The deleterious effects of TBI can be aggravated by a diet high in saturated fat. These changes may underlie synaptic dysfunction and cognitive impairment observed after TBI. Free radical scavengers such as vitamin E and curcumin can counteract the deleterious effects of cumulative free radicals on cognitive function and synaptic plasticity encountered in TBI.

with nucleophiles such as glutathione. Hence, curcumin has the potential to inhibit lipid peroxidation and neutralize reactive oxygen and nitric-oxide-based free radicals (Butterfield and Lauderback, 2002). Another critical characteristic of curcumin is the capacity of crossing the blood–brain barrier to produce its neuroprotection directly (Yang et al., 2005).

These findings are coherent with our previous results showing that another antioxidant, i.e., vitamin E, can reduce the deleterious effects of elevated oxidative stress associated to the consumption of a diet high in saturated fat (Wu et al., 2004a). Accordingly, to evaluate the full strength of the antioxidant capacity of curcumin, we tested the effects of curcumin in animals that were exposed to a high-fat diet. Results showed that curcumin treatment counteracted the effects of combined applications of high-fat diet and FPI in all experimental conditions. These findings emphasize the risk factor imposed by certain diets and the therapeutic capacity of others to counteract these effects. The therapeutic value of dietary supplementation of curcumin can be particularly effective under challenging conditions. Recently, we have reported that dietary supplementation of omega-3 fatty acids, which also possess antioxidant capacity, can improve neurological recovery after TBI using a BDNF-mediated mechanism (Wu et al., 2004b).

Supplementation with curcumin in the diet affects cognition and synaptic plasticity by modulating the BDNF system

Our finding that supplementation of curcumin normalizes the protein levels of BDNF after TBI suggests that BDNF mediates the beneficial effects of curcumin on cognitive function. We have recently shown that TBI impairs cognitive function and that this seems to be associated with low levels of BDNF and of its downstream effectors in synaptic plasticity synapsin I and CREB (Wu et al., 2003). BDNF can modulate 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 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; Wilson et al., 2004). Hippocampal BDNF seems necessary for the induction of LTP (Korte et al., 1995; Linnarsson et al., 1997; Patterson et al., 1996). 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). Based on discussed evidence, it is possible that dietary supplementation of curcumin may provide protection against cognitive impairment after TBI through counteracting the harmful effects of oxidative stress and by up-regulating the expression of molecular systems related to BDNF. In spite of the strong antioxidant capacity of curcumin, we cannot discard the possibility that curcumin may also provide neuroprotection by other mechanisms such as by reducing inflammation. Although further research is required, it seems feasible that

the therapeutic effects of curcumin on cognition in TBI rats may be associated with the function of BDNF.

Conclusions

We provided evidence supporting the harmful impact of oxidative stress on synaptic plasticity and cognitive function after TBI, using a mechanism centered on the action of BDNF. The powerful antioxidant effects of curcumin were sufficient to reduce the action of oxidative stress on the BDNF system, synaptic plasticity, and cognitive function. Our findings suggest that curcumin supplementation might be an effective therapy to counteract the deleterious effects of TBI on neuronal plasticity and function.

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