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RESEARCH ARTICLE

Continuous exercise training and curcumin attenuate changes in brain-derived neurotrophic factor and oxidative stress induced by lead acetate in the hippocampus of male rats

Somayeh Hosseinzadeh[1], Valiollah Dabidi Roshan[2], and Soleiman Mahjoub[3]

[1]Babol University of Medical Sciences, Babol, Iran, [2]College of Physical Education and Sport Sciences, Department of Sport Physiology, University of Mazandaran, Babolsar, Iran, and [3]Department of Biochemistry & Biophysics, Babol University of Medical Sciences, Babol, Iran

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Abstract

Context: For many years it has been known that lead is life-threatening, not only as an air pollutant but also because of it has been associated with several conditions including neurodegenerative disease. Curcumin (the principal curcuminoid found in turmeric) has demonstrated potent antioxidant properties.

Objective: We investigated neuroprotective effects of endurance exercise and/or curcumin on lead acetate-induced neurotoxicity in the rat hippocampus.

Materials and methods: Forty male Wistar rats were randomly divided into five groups: 1) lead acetate, 2) curcumin, 3) training, 4) training + curcumin, and 5) control. The rats in the training groups performed treadmill running five times a week for 8 weeks (15–22 m/min, 25–64 min). All groups except control received lead acetate (20 mg/kg), whereas the control group received curcumin solution (ethyl oleate). In addition, the curcumin and training + curcumin groups received curcumin solution (30 mg/kg) intraperioneally.

Results: Lead acetate resulted in a significantly increase in the malondialdehyde (MDA) in plasma (72%), but not significant in hippocampus (59%). In addition, it led to significantly decreased brain-derived neurotrophic factor in hippocampus (17%) and total antioxidant capacity (27%), as compared to control group. Treadmill running, curcumin supplementation or both resulted in a significant decrease in hippocampus MDA (17, 20, 31%, respectively) and plasma MDA (60, 22, 71%) and also, significantly increased brain-derived neurotrophic factor (76, 45, 94%) and total antioxidant capacity (47.13, 47.11, 61%) levels, as compared to lead acetate group.

Discussion and Conclusion: These results provide a rationale for an inhibitory role of curcumin and regular exercise in the attenuation of lead-induced neurotoxicity.

Keywords: Endurance exercise, antioxidant, neurotoxicity, lipid peroxidation, air pollution, neurotherophic factors

Introduction

Epidemiological studies have established a link between ambient air pollutants and health (Makria & Stilianakis, 2008). Lead is a ubiquitous environmental and industrial pollutant that induces a broad range of physiological, biochemical, and behavioral abnormalities in both laboratory animals and humans, including central and peripheral nervous system dysfunction (Hsu & Guo, 2002). It has now become clear that high to moderate doses of lead exposure stimulate free radicals, resulting in oxidative damage to critical biomolecules, lipids, proteins and DNA, as well as adversely affect antioxidant defense systems of cells (Migliore & Coppedè, 2009). The depletion and changes in the activity of various antioxidant enzymes indicative of lipid peroxidation have been implicated in lead-induced oxidative tissue damage (Ahamed et al., 2007). Brain tissue is particularly vulnerable to apoptosis due to oxidative stress of ROS

Address for Correspondence: Valiollah Dabidi Roshan, College of Physical Education and Sport Sciences, Department of Sport Physiology, The University of Mazandaran (UMZ) Pasdaran Street, 47415, P.O. Box: 416, Babolsar, Iran. Tel: +98 (0) 11252 32091-95. Fax: +98 (0) 1125342202 or/ +98 (0) 11252 32017-33702. E-mail: vdabidiroshan@yahoo.com

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related to various factors such as high-level utilization of oxygen in the presence of relatively weak antioxidant defense systems and complex chemical reactions for production of diverse neurotransmitters (Oiae & Park, 2008). Studies with humans show that blood lead levels, even at 10 μg/dL, may cause cognitive deficits (Shukla et al., 2003). The brain region, including hippocampus, not only plays a major role in memory and learning, but produces neurons during the process of growing. An increased production of ROS has a high possibility of degrading neurons in the hippocampus and deteriorating cognitive and memory functions (Oiae & Park, 2008).

Lifestyle factors such as diet and exercise may provide beneficial effects on hippocampus function. Oiae & Park, 2008 suggested that regular exercise training increased the production of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), especially in the hippocampus, a major hub for learning and memory formation (Soya et al., 2007). BDNF is one of the most versatile and important neurotrophic factors in the brain. It plays a critical role in the learning process, memory, locomotion, behavior, and a wide range of stress responses. Furthermore, it has been reported that increased BDNF is related to improved cognitive function. It has been suggested that regular exercise could strengthen antioxidant protection of the hippocampus and BDNF mediates the protection of neurons, which in turn, protects oxidative stress of the hippocampus caused by ROS (Oiae & Park, 2008). On the other hand, over thousands of years, diet, in conjunction with other lifestyle factors, such as exercise, have had a crucial role in shaping cognitive capacity and brain evolution (Gomez-Pinilla, 2008a). Polyphenols are natural substances that are present in plants, fruits and vegetables including olive oil and tea. Turmeric contains a class of compounds known as the curcuminoids, comprised of curcumin, demethoxycurcumin and bisdemethoxycurcumin. Curcumin (the principal curcuminoid found in turmeric) comprises approximately 2–5% of turmeric and is generally considered its most active constituent. It is responsible for the yellow color of the spice as well as the majority of turmeric's therapeutic effects (Wilken et al., 2011). Curcumin is non-toxic and has antioxidant, anti-inflammatory and anti-proliferative activities. Curcumin shows antioxidant activity equivalent to vitamins C and E (Ataie et al., 2010).

Despite the fact that lead can induce oxidative stress, these studies have only identified effects of exercise and/or antioxidants on mental health without considering air pollutants. Moreover, there is less information with respect to simultaneous effects of lifestyle, including aerobic regular training, antioxidant supplementation, or both, on oxidant/antioxidant process and brain function during chronic exposure to lead acetate. Therefore, the purpose of this study was to determine the effects of aerobic exercise, curcumin supplementation, or both, on BDNF in the hippocampus and also on biomarkers of oxidative stress [total antioxidant capacity (TAC) and malondialdehyde (MDA)] in plasma and hippocampus of rats chronically exposed to lead acetate.

Methods

Animals and experimental environment

The experimental protocol was approved by Department of Physiology, University of Mazandaran and was performed according to guiding procedures in the Care and Use of Animals, prepared by the Council of the American Physiological Society. Forty male Wistar rats, 8 weeks of age (initial body weight of 240 ± 20 g), were obtained from the Laboratory of Animal Bearing and Multiplying at the Pasture Institute of Iran. Each rat was housed in single standard cages of polycarbonate (20 × 15 × 15), made at the Pasture Institute of Iran, in a large air-conditioned room with a controlled temperature of 22 ± 2°C, light-dark cycles 12:12 h and humidity of 50 ± 5%. Measurements from the pollution determination station of the Iranian Meteorological Organization determined that the pollutant standard index (PSI) was in the normal range. Rats were fed with a standard rat chow provided by Pars Institute for Animal and Poultry with a daily regimen of 10 g per 100 g body weight for each rat. Water was available *ad libitum*.

Experimental procedures

Rats were familiarized with the laboratory environment and running on the treadmill, and then were randomly assigned into five experimental groups of eight rats as follows: Group 1 – lead acetate (Pb), exposed to lead at a concentration of 25 mg/kg in the form of a water solution of lead acetate (for intraperitoneal injection), 3 days weekly for 8 weeks; Group 2 – Pb + curcumin (Cum), received curcumin 30 mg/kg 5 days weekly, for 8 weeks (i.p.), in addition to lead acetate; Group 3 – endurance training (Pb + training), the rats in this group similarly received lead acetate and in addition they performed progressive running exercise of 15 to 22 m/min for 25 to 64 min, five times a week; Group 4 – training and curcumin (Pb + training + Cum); rats in this group performed the same training protocol described above and in addition received lead acetate and curcumin supplementation; Group 5 – sham-operate or control group (sham); these rats received water and ethyl oleate, in the same manner and for the same duration of time as the other groups.

Exercise training

All rats were acclimatized to ambient rearing conditions for 4–5 days in group housing conditions (four rats per cage) and then habituated to run on a treadmill (KN-73, Natsume Ltd., Japan) five sessions in first week. Thus, the running speed and time was gradually increased from 15 to 22 m/min and from 25 to 64 min. At the end of the belt were stationary wire loops, which were electrified. A mild shock (0.75 mA, 500 ms duration, 0.5 Hz rate) was delivered through these loops to motivate the rats to continuously walk on the moving belt and thus avoid foot shock. The wire loops were activated during all exercise

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sessions, and an experimenter monitored all treadmill sessions. Rats quickly learned to stay on the belt and avoid shock, except for one rat, which would not stay on the moving belt, and thus was quickly removed from the exercise group.

Lead acetate and curcumin supplementation

We are replicating a previously reported lead dosing regimen that caused oxidative stress; thus, the doses of curcumin (the principal curcuminoid found in turmeric) and lead acetate were 30 and 20 mg/kg, respectively (Daniel et al., 2004). Lead acetate (Sigma) was solubilized in Milli-Q water, and curcumin was solubilized in 50% ethanol. In order to perform intra-peritoneal (i.p) injections, curcumin was solubilized in ethyl oleate and was injected at a dose of 30 mg/kg. Curcumin was protected from light during the time of the experiment (Daniel et al., 2004).

Sampling and tissue collection

After 8 weeks of treatment for each group followed by 24 h of resting and after 12–14 h overnight fasting, the animals were anesthetized after injection mixture of xylazine and katamine intraperitoneal (i.p.). Cardiac blood samples were collected 24 h after the last dose of treatment. The blood samples were first centrifuged at 3,000 rpm for 15 min within 30 min of collection, and then stored at –80°C before assay and serum was separated for biochemical estimations of TAC and MDA. Brains were rapidly removed and the two hemispheres separated along the midline. The hippocampus from each hemisphere was then micro-dissected and frozen in liquid nitrogen and subsequently stored at –80°C for future analysis.

Analyses of markers

BNDF assay

For protein extraction, the hippocampus was homogenized in a lysis buffer (18 ml/mg tissue) containing 137 mM NaCl, 20 mM Tris–HCl (pH 8.0), 1% NP 40, 10% glycerol, 1 mM PMSF, leupeptin (1 mg/ml), sodium vanadate (0.5 mM), and AEBSF (100 mg/ml) (Adlard et al., 2005). Samples were then centrifuged for 3 min (14000 rpm, 3 min, 4°C) and supernatant collected and stored at –20°C. The BDNF protein level was determined by a BDNF ELISA kit according to the manufacturer's recommendations.

MDA assay

Lipid peroxidation levels in the tissue homogenate were measured with a thiobarbituric-acid reaction by the method of Ohkawa et al. (1979). Sample homogenates (1 ml) were incubated at 37°C in an oscillating water bath for 1 h. At the end of the incubation period, 0.5 ml of BHT (0.5 mg/ml in absolute ethanol) and 1 ml of TCA (25%) were added. The tubes were sealed and heated for 10 min in a boiling water bath to release MDA (the end product of lipid peroxidation) from proteins. To avoid adsorption of MDA to insoluble proteins, the samples were cooled to 4°C and centrifuged at 2000 g for 20 min. Following centrifugation, 2 ml of the protein free supernatant was removed from each tube and 0.5 ml of TBA (butylhldroxytoluene) (0.33%) was added to this fraction (Daniel et al., 2004). All tubes were heated for 1 h at 95°C in a water bath. After cooling, the TBA-MDA complexes were extracted with 2 ml of butanol. The light absorbance was read at 532 nm on a spectrophotometer and MDA levels were determined from a standard curve that was generated from 1,1,1,3-tetramethoxypropan. The results are represented as nmol/mg tissue.

TAC assay

Serum TAC was measured using a commercially available kit (Randox Laboratories, Crumlin, UK) as previously described (Erel, 2004). In this method, the most potent radical, hydroxyl radical, is produced. First, a ferrous ion solution is mixed with hydrogen peroxide. The sequentially produced radicals such as brown colored dianisidinyl radical cations, produced by the hydroxyl radical, are potent radicals. The antioxidative effect of the sample against the potent free radical reactions is then measured. The assay has excellent precision values, which are lower than 3%. The results are expressed in μmol/mL. The concentration of lead was detected by means of atomic absorption spectrophotometry (AAS).

Statistical analysis

Statistical analysis was performed using a commercial software package (SPSS version 16.0 for Windows). Results are expressed as means ± SE. Data for BDNF and oxidant/antioxidant markers were normally distributed after log transformation. A one-way ANOVA was used to detect statistical difference between groups. Tukey tests were performed to assess differences in the mentioned markers between groups. The differences were considered significant at $p < 0.05$.

Results

Mean values for body mass, brain mass, and brain-body mass ratio levels in rats chronically exposed to lead acetate are shown in Table 1. A significant decrease in body mass and a trend for a decrease in brain mass was detected after lead acetate administration (20 mg/kg), as compared to the other groups. Aerobic training and curcumin supplementation protocols during chronic exposure to lead acetate caused preservation in body and brain mass (Table 1).

Changes in BDNF levels in the hippocampus, plasma TAC, and MDA in both hippocampus and plasma in the lead-exposed rats are shown in Table 2. The administration of lead at the concentration of 20 mg/kg for 8 weeks resulted in a decrease in TAC and BDNF levels by 27 and 17% as compared to the control group, respectively. In contrast, curcumin and/or exercise training significantly increased the TAC in plasma (47%) and the BDNF in hippocampus (45 and 76%) levels, as compared to lead acetate group. The mixture of training and curcumin was more effective than curcumin + lead and/or training + lead alone treatment (Figures 1 and 2).

Table 1. Effectiveness of the 8-week training and supplementation protocols on body mass, brain mass and brain-body mass ratio in rats chronically exposed to lead acetate.

Markers	SH	L	TL	CL	TCL
Body mass (g)	341 ± 33[a]	306 ± 33	328 ± 20[a]	322 ± 22	343 ± 34[a]
Brain mass (g)	1.738 ± 0.149	1.618 ± 0.192	1.765 ± 0.209	1.723 ± 0.101	1.794 ± 0.185
Brain-bodymass ratio	0.0051 ± 0.005	0.0053 ± 0.006	0.0049 ± 0.011	0.0054 ± 0.005	0.0052 ± 0.054

Values are means ± standard deviation for eight rats.
CL, (Curcumin + Lead); SH, (Sham); L, (Lead); TL, (Training + Lead); TCL, (Training + Curcumin + Lead) groups.
[a]Significant compared with lead acetate group.

Table 2. Effect of exercise training and curcumin on BDNF, TAC, and MDA in plasma and hippocampus levels in lead-induced rats (mean ± SEM for eight rats).

Group	BDNF hippocampus (ng/ml pro.)	TAC plasma (μ mol/mL)	MDA hippocampus (nmol/mg pro.)	MDA plasma (nmol/mg pro.)
Sham	1.80 ± 0.65	385.75 ± 8.90	0.34 ± 0.27	26.82 ± 2.85
Lead	1.54 ± 0.2	279.86 ± 18.33	0.54 ± 0.12	46.09 ± 9.22
Training + lead	2.71 ± 1.66	411.75 ± 13.87	0.45 ± 0.16	18.41 ± 3.28
Curcumin + lead	2.24 ± 1.29	411.71 ± 14.81	0.43 ± 0.11	35.83 ± 6.49
Curcumin + training + lead	2.99 ± 1.83	450.37 ± 19.74	0.37 ± 0.13	13.36 ± 2.54

BDNF, brain-derived neurotrophic factor; MDA, malondialdehyde; TAC, total antioxidant capacity.

On the other hand, administration of lead acetate (20 mg/kg) caused an increase in the concentration of hippocampus and plasma MDA by 59 and 72%, as compared to the control group, respectively. In contrast, curcumin and/or exercise training insignificantly decreased the MDA in hippocampus (20, 17%, respectively) and significantly decreased in plasma (22, 60%, respectively), as compared to lead acetate. However, co-treatment with curcumin and training was more effective to decrease lead-induced MDA than the other two treated groups (Figures 3 and 4).

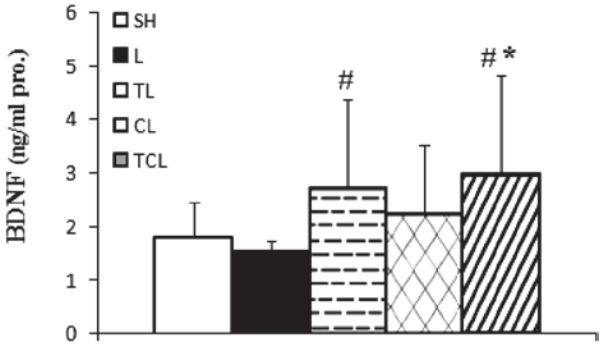

Figure 1. The brain-derived neurotrophic factor concentration in hippocampus in rats chronically exposed to lead acetate. Values are means ± SD. SH, (Sham); L, (Lead); TL, (Training + Lead); CL, (Curcumin + Lead); TCL, (Training + Curcumin + Lead) groups. Statistical significance $p < 0.05$: *Significant than sham group, #Significant than lead group.

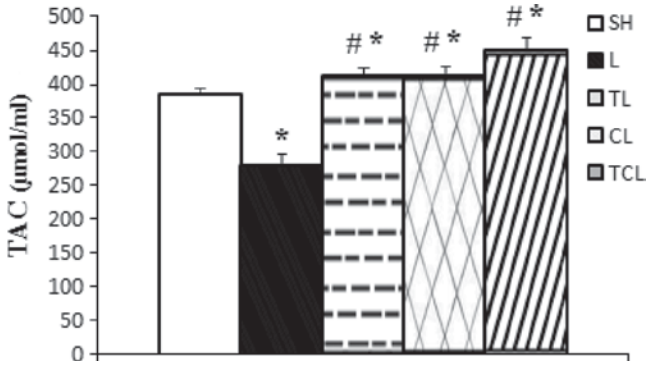

Figure 2. Concentration of total antioxidant capacity in plasma in rats chronically exposed to lead acetate. Values are means ± SD; SH, (Sham); L, (Lead); TL, (Training + Lead); CL, (Curcumin + Lead); TCL, (Training + Curcumin + Lead) groups. Statistical significance $p < 0.05$: *Significant than sham group, #Significant than lead group.

Discussion

Air pollution is a complex mixture of environmental toxins, such as lead, that assault the CNS through several cellular and molecular pathways to cause disease (Block, 2009). The present study demonstrates a protective effect of regular exercise and curcumin supplementation against lead neurotoxicity in the hippocampus of rats that were chronically exposed to lead acetate. Enhancement of MDA associated with reduced TAC and BDNF may lead to neurodegenerative conditions resulting from lead toxicity via disrupting oxidant/antioxidant balance, whereas lifestyle factors such as regular exercise and curcumin supplementation reverse this process through increasing BDNF and improving antioxidant defense systems. Other recent studies have linked environmental exposures causing oxidative stress with neurodegenerative diseases and aging (Migliore & Coppedè, 2009). Pb causes significant changes in oxidative stress in different brain regions, particularly in the hippocampus and cerebral cortex which are found to be more vulnerable to Pb-induced neurotoxicity (Prasanthi et al., 2010). Several mechanisms, including cholinergic dysfunction, glutamate receptor alterations, impaired antioxidant defense enzymes in the brain and enhanced oxidative stress, have been suggested to be causative factors with lead neurotoxicity (Shukla et al., 2003). Others have suggested that oxidative stress caused by lead is associated with disrupted prooxidant/antioxidant balance (Hsu & Guo, 2002). Generation of highly reactive oxygen species

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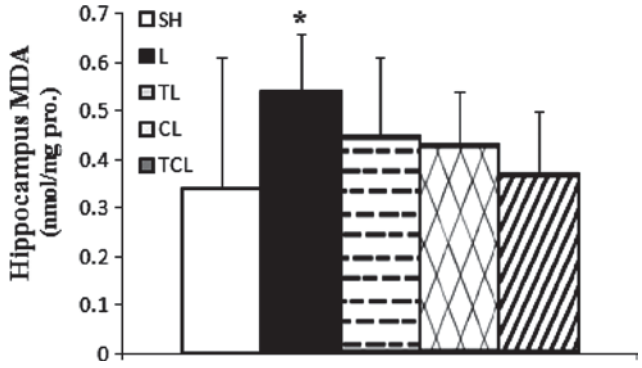

Figure 3. Concentration of the hippocampus malondialdehyde (MDA) in rats chronically exposed to lead acetate. Values are means ± SD; SH, (Sham); L, (Lead); TL, (Training + Lead); CL, (Curcumin + Lead); TCL, (Training + Curcumin + Lead) groups. Statistical significance $p < 0.05$; *Significantly than sham group.

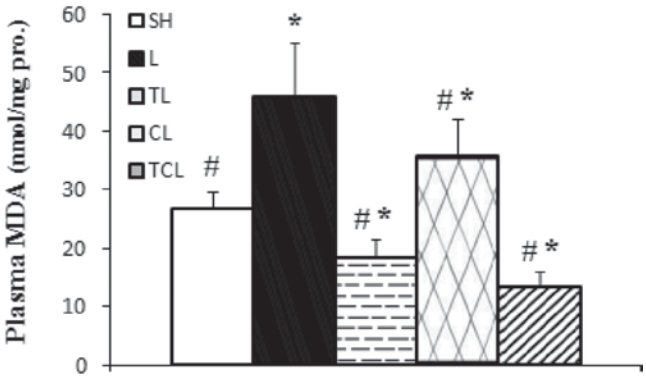

Figure 4. Concentration of malondialdehyde (MDA) in plasma in rats chronically exposed to lead acetate. Values are means ± SD; SH, (Sham); L, (Lead); TL, (Training + Lead); CL, (Curcumin + Lead); TCL, (Training + Curcumin + Lead) groups. Statistical significance $p < 0.05$; *Significant than sham group, #Significant than lead group.

in the aftermath of lead exposure may result in systematic mobilization and depletion of the cell's intrinsic antioxidant defenses. Lipid peroxidation appears to be markedly enhanced in the brain of lead-treated rats (Antonio-Garcia & Massó-Gonzalez, 2008), which concurs with our findings of decreased production of TAC and increased MDA.

The ability of specific aspects of lifestyle such as diet, exercise and other factors that modulate mental function is becoming increasingly recognized. There is evidence to suggest regular exercise improves brain function and leads to structural, biochemical, and physiological adaptations through a variety of pathways. Exercise counteracts deteriorative effects on the central nervous system caused by inactivity. High levels of ROS exceed the adaptive tolerance of cells, resulting in significant oxidative damage, apoptosis, and necrosis. Studies have shown an exercise-induced regulation of BDNF transcripts in the rat hippocampus and postulated that it may help to increase the brain's resistance to damage and neurodegeneration that occurs with aging (Strasser et al., 2006). Exercise training likely results in an increase in antioxidant defenses such as TAC and thus increased resistance and tolerance to oxidative challenges. Although some studies suggest that exercise training enhances antioxidant capacity, the causal mechanisms are not known. It has also been shown that high intensity endurance exercise increases susceptibility to oxidation; a training regimen at 65% VO_2 max has also been reported to decreases plasma TAC in rats (Alipour et al., 2006). Interestingly, a dose-response relationship between exercise duration/intensity and health-related quality of life has been reported, in which the best outcomes are associated with moderate exercise (Cotman et al., 2007; Soya et al., 2007). This variability is probably related to differences in the exercise regimen (voluntary versus forced), in combination with the intensity (in forced exercise models) and duration of exercise exposure. In addition, although some studies show improvements after 1 week of exercise, most benefits have been associated with longer-term exercise (3–12 weeks) (Cotman et al., 2007).

Dietary factors can affect multiple brain processes by regulating neurotransmitter pathways, synaptic transmission, membrane fluidity, and signal-transduction pathways. The curry spice curcumin, a traditional food preservative and medicinal herb in India, is relatively non-toxic and has few side effects at doses greater than the low doses that have been tested in mice. Despite concerns about poor oral bioavailability, curcumin has at least 10 known neuroprotective actions. Accumulating cell culture and animal model data show that dietary curcumin is a strong candidate for use in the prevention or treatment of major disabling age-related neurodegenerative diseases like Alzheimer's, Parkinson's, and stroke (Cole et al., 2007). It is a strong antioxidant that seems to protect the brain from lipid peroxidation and nitric-oxide-based radicals (Gomez-Pinilla & Kostenkova, 2008b). Interestingly, curcumin not only exhibits antioxidative and free radical scavenging properties, but it also increases the activities of other antioxidant enzymes, such as SOD, CAT, and GPx (Agarwal et al., 2010). An increasing number of studies have shown that curcumin may be neuroprotective. Gomez-Pinilla recently found that curcumin, as a dietary supplement, counteracts cognitive dysfunction resulting from elevated ROS after brain trauma (Gomez-Pinilla, 2008c). Curcumin also produces marked increases in BDNF levels in the brains. Accordingly, when dietary supplementation and exercise are combined, inhibition of lead-induced antioxidant/oxidant imbalance, increases in BDNF, and decreases in hippocampus oxidative stress appear to be more pronounced than when either intervention is implemented by itself.

Conclusions

In summary, our study provides a rationale for the inhibitory role of curcumin and regular exercise in attenuating lead-induced neurotoxicity. Treatment with exercise and/or curcumin reduced the accumulation of lead-induced oxidative stress in rat hippocampus. Moreover,

the combination of training and curcumin can make the brain more resistant to oxidative damage than curcumin + lead and or/training + lead alone treatment.

Declaration of interest

The authors declare no conflicts of interest.

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