Turkish Journal of Geriatrics
2010; 13 (3) 160-165

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RESEARCH

CURCUMIN REDUCES OXIDATIVE STRESS IN OVARIECTOMIZED RAT BRAIN SUBJECTED TO CHRONIC CEREBRAL HYPOPERFUSION

ABSTRACT

Introduction: Curcumin, the major constituent of turmeric, exhibits both antioxidant and anti-inflammatory activities. In the present study, we investigated whether or not curcumin reduces oxidative stress in ovariectomized female rat brain by using a model of chronic cerebral hypoperfusion.

Materials and Method: Chronic cerebral hypoperfusion was induced by permanent ligation of both common carotid arteries. Animals (a total of 30 adult female Wistar Albino rats, 4-6 months old) were randomly divided into three groups: sham control, ischemia, and ischemia plus daily curcumin treatment (100 mg/kg) for 14 days. At day 14 after the ligation, malondialdehyde (MDA) and reduced glutathione (GSH) contents of brain tissues were measured in all groups.

Results: Ischemia caused a significant increase in MDA content but a meaningful decrease in GSH levels. Treatment with curcumin, however, lowered MDA and elevated GSH contents significantly in ischemic brain tissue, bringing their levels back to that of the sham group.

Conclusion: Our results suggest that curcumin attenuates both oxidative stress and lipid peroxidation in chronic cerebral hypoperfusion, which is an animal model of vascular dementia. Following further in depth investigations into underlying molecular mechanism(s), we believe that therapeutic efficacy of curcumin deserves to be tested for potential clinical application especially in postmenopausal elderly women suffering from vascular dementia.

Key Words: Curcumin; Chronic cerebral hypoperfusion; Oxidative stress.

ARAŞTIRMA

KURKUMİN KRONİK SEREBRAL HİPOPERFÜZYONA MARUZ KALMIŞ OVEREKTOMİLİ SIÇAN BEYİN DOKUSUNDA OKSİDATİF STRESİ AZALTMAKTADIR

ÖZ

Giriş: Turmeriğin majör komponenti olan kurkumin hem antioksidan hem de antiinflamatuar aktivite göstermektedir. Çalışmamızda, kronik serebral hipoperfüzyon modelini kullanarak, overleri alınmış dişi sıçan beyininde, kurkuminin oksidatif stresi azaltıp azaltmadığını araştırdık.

Gereç ve Yöntem: Kronik serebral hipoperfüzyon, her iki karotid komunis arterin kalıcı ligasyonu ile sağlandı. Denekler (4-6 aylık toplam 30 adet yetişkin Wistar Albino dişi sıçanlar) rastgele üç gruba ayrıldı: sham kontrol, iskemi ve 14 gün boyunca günlük kurkumin (100 mg/kg) verilen iskemi grubu. Ligasyon sonrası 14üncü günde tüm gruplardaki beyin dokularının malondialdehid (MDA) ve indirgenmiş glutatyon (GSH) içerikleri ölçüldü.

Bulgular: İskemi, MDA içeriğinin ileri dercede yükselmesine neden olurken GSH seviyesini anlamlı derecede azalttı. Diğer yandan, kurkumin tedavisi iskemik beyin dokusunda anlamlı derecelerde MDA düzeyini düşürerek ve GSH içeriğini yükselterek, değerlerin sham grubundakiler seviyesine geri dönmesini sağladı.

Sonuç: Elde ettiğimiz sonuçlar, vasküler demansın deneysel hayvan modeli olan kronik serebral hipoperfüzyonda kurkuminin hem oksidatif stresi hem de lipid peroksidasyonunu azalttığını önermektedir. Altta yatan moleküler mekanizmaların derinlemesine daha fazla araştırılması sonrasında inanıyoruz ki kurkuminin tedavideki verimliliği, klinik uygulamalar için özellikle de vasküler demanslı menopoz sonrası yaşlı kadınlarda test edilmesine layık olacaktır.

Anahtar Sözcükler: Kurkumin; Kronik serebral hipoperfüzyon; Oksidatif stres.

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Geliş Tarihi: 28/06/2009
(Received)

Kabul Tarihi: 08/09/2009
(Accepted)

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INTRODUCTION

Cerebrovascular diseases, manifesting cerebral arteriosclerosis and infarction, result in chronic cognitive impairment, which constitutes the second most common form of dementia in the elderly: vascular dementia (1,2). A persistent decrease in cerebral blood flow is observed not only in Alzheimer's disease (AD) but also in vascular dementia and post-stroke hypoperfusion. Decreased cerebral blood flow correlates well with the extent of memory impairment (3). Recent studies show that decrease in cerebral blood flow precedes onset of vascular dementia and that chronic cerebral hypoperfusion may be a trigger for vascular dementia and the accompanying cognitive decline (1,4). Permanent occlusion of both common carotid arteries generates a moderate but chronic ischemia associated with cognitive alterations and neuronal degeneration in rats. The model has been a valuable tool that provides insight into the pathophysiology of chronic cerebrovascular disorders in general and of vascular dementia in particular (2,4). A number of different biochemical pathways and mechanisms appear to participate in development of hypoxic-ischemic brain injury. Oxidative stress has an especially important contribution to hypoperfusion-induced neuronal damage (2,5-7).

During menopause, ovarian estrogen production ceases, potentially influencing functions of the central nervous system (CNS). Moreover, women are dramatically affected by various neurological disorders during postmenopausal ages, such as memory loss, mild cognitive impairment, ischemic stroke, Parkinson's disease, and AD (8,9). Acute loss of ovarian hormones were reported to cause damage to neuronal membranes. Furthermore, suppression of ovarian function correlates with reduced activation of brain regions that are associated with memory processing (10).

Curcumin, a yellow-orange dye extracted from the spice turmeric, has many beneficial effects such as anti-inflammation, anti-oxidation, and anti-carcinogenesis (11-13). Several animal studies show that curcumin has neuroprotective effects in both global (14) and focal (11,15,16) cerebral ischemia. Several lines of work also demonstrate that curcumin has free radical scavenging activity; thus, protecting against reactive species (11,17). Moreover, curcumin could prevent or reduce oxidative stress-induced progression of age-related neurodegenerative disorders such as AD (17).

Pharmacological treatment of cognitive disorders in dementia has been lacking despite extensive efforts for effective therapy at both neuronal and vascular level. Targeting vascular mechanisms in dementia may be an important therapeutic option (18). Recent studies have focused mainly on dietary antioxidants and plant-derived polyphenolic compounds for preventing neurons from harmful effects of both aging and other neurodegenerative processes. The second most common cause of cognitive impairment and dementia is stroke. Diagnosing stroke promptly and determining an appropriate treatment that can help or substantially delay onset and progression of cognitive impairment/dementia, has been quite a challenge. Previous studies demonstrated that curcumin exhibits remarkable neuroprotective effects in global and focal cerebral ischemia through its antioxidant and anti-inflammatory effects. On the other hand, the effect of curcumin on oxidant status in chronic cerebral hypoperfusion has not been reported so far. The purpose of the present study is, therefore, to evaluate whether long term administration of curcumin could attenuate oxidative stress induced by chronic cerebral hypoperfusion in ovariectomized female rats. Based on the previous studies in literature, the model used in the present study mimics vascular dementia in postmenopausal women.

MATERIALS AND METHOD

Animals

A total of 30 adult female Wistar Albino rats (4-6 months old, 200-250 g) were used for the experiments. At 4 to 6 weeks prior to the study, animals were bilaterally ovariectomized under ketamine (70 mg/kg, i.p.) anesthesia to eliminate endogenous estradiol and progesterone production. Animals were maintained in their cages at constant room temperature using a 12 h: 12 h light/dark cycle and housed under standard conditions. All protocols followed in the present study were approved by the animal care and use committee of the institution where the work was carried out. Animals had free access to food and water before and after surgery.

Surgery

Chronic cerebral hypoperfusion was generated by bilateral ligation of common carotid arteries. Following anesthesia with ketamine (90 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.) a midline cervical incision was made in which both common carotid arteries were exposed and gently separated from carotid sheath and vagus nerve. Then, in the ischemic groups, each artery was ligated with a 5/0 silk suture. In the sham control group, animals were subjected to the same operation without ligation. The rectal temperature was maintained at 37 ºC during the surgical procedure with a heating lamp. After the surgical operation, rats were kept in cages with food and water ad libitum.

Experimental Design

Rats were randomly divided into groups of sham, ischemia and ischemia treated with curcumin (100 mg/kg). Once-daily

oral administration of curcumin was started on day 1 and terminated on the day of sacrificing (day 14). On day 14, brain tissues were carefully collected and stored at 40 ºC. In the treatment procedure, curcumin was mixed with peanut butter, while animals in control groups received only peanut butter. All animals showed remarkable adjustment for eating the newly introduced food. The curcumin dosage was based on previous studies showing its neuroprotective effects in the rat model of focal cerebral ischemia (14,16).

Biochemical Analysis

Oxidant and antioxidant status of rat brain subjected to hypoperfusion was assessed by measuring levels of lipid peroxidation and reduced glutathione (GSH).

Lipid peroxidation was evaluated by measuring the level of malondialdehyde (MDA), a by-product of lipid peroxidation (19). Briefly, by using a motor-driven pestle, tissue samples were homogenized in ice-cold trichloroacetic acid (TCA) by adding 10 ml of 10% TCA per 1g of tissue. After centrifugation, 750µl supernatant was added to an equal volume of 0.67% thiobarbituric acid and heated to 100 °C for 15 min. The absorbance of the samples was measured spectrophotometrically at 535 nm.

The GSH content of the samples was measured by a modified Ellman method (20). To the 0.5 ml of supernatant obtained by using the same homogenization procedure as described above, 2 ml of 0.3 M Na_2HPO_4 solution was added. A 0.2 ml solution of dithiobisnitrobenzoate was added into the mixture, and the absorbance at 412 nm was measured immediately after vortexing.

Data Analysis

Each data point represents mean ± S.E.M. (n = 10 for each group in all experiments). For statistical evaluation, SPSS 11.0 statistical software package program was used (SPSS Inc., Chicago, IL, USA). One-way analysis of variance (ANOVA) was applied for statistical comparison of groups, followed by analysis with post-hoc Tukey test to determine differences between the groups. Probability values of 0.05 or less were considered statistically meaningful.

RESULTS

Ischemia increase the average MDA content significantly (75.14 ± 5.63 nmol/g tissue) compared to that measured in the sham group (44.97 ± 4.79 nmol/g tissue). However, treatment with curcumin significantly reduced the MDA content of the cerebral tissue to control levels, averaging 54.35 ± 6.41 nmol/g tissue (Figure 1, Table 1).

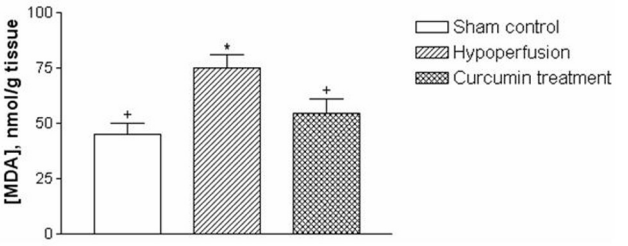

Figure 1— Effect of curcumin on lipid peroxidation of brain tissue subjected to chronic cerebral hypoperfusion. Data is shown as mean ± S.E.M. (n = 10). "*" and "+" ($p < 0.05$) indicate statistical significance compared to sham and hypoperfused groups, respectively.

Table 1— Values of MDA and GSH, Measured in Each Experimental Group as Mean ± SE

Groups	MDA nmol/g tissue	GSH umol/g tissue
Sham control (n=10)	44.97 ± 4.79[a]	0.61 ± 0.02[a]
Ischemia (n=10)	75.14 ± 5.63[b]	0.28 ± 0.03[b]
Curcumin-treated ischemia (n=10)	54.35 ± 6.41[c]	0.66 ± 0.06[c]

Analysis with Tukey post hoc test. (a,b), (b,c) $p < 0.05$.

Average GSH content of the tissues in the ischemia group was approximately 46% of that of the sham control group (0.28 ± 0.03 vs. 0.61 ± 0.02 mmol/g tissue) and the difference between the groups were statistically meaningful ($p < 0.01$) (Figure 2). Average GSH contents in sham control and curcumin-treated animals (0.66 ± 0.06 mmol/g tissue) were indistinguishable ($P = 0.70$). The treatment caused a remarkable increase in the GSH content (Table 1).

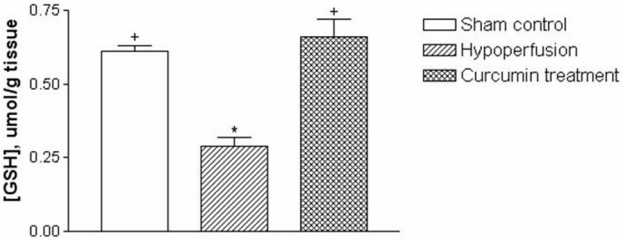

Figure 2— Effect of curcumin on GSH content of brain tissue subjected to chronic cerebral hypoperfusion. Data is shown as mean ± S.E.M. (n = 10). "*" and "+" ($p < 0.05$) indicate statistical significance compared to sham and hypoperfused groups, respectively.

Discussion

The present study demonstrates that postischemic treatment with curcumin prevents oxidative stress and lipid peroxidation in brain tissue of rats subjected to chronic cerebral hypoperfusion. We evaluated tissue MDA levels produced by peroxidation of unsaturated fatty acids in cell membranes. This biochemical reaction is catalyzed by free radicals produced by ischemia (i.e. chronic hypoperfusion). We also examined tissue content of GSH which plays an important role in protection against ischemic neuronal injury caused by oxidative stress. Postischemic curcumin administration (100 mg/kg, p.o.) prevented not only depletion of GSH but also elevation of MDA content. In another words, curcumin reduced both oxidative stress and lipid peroxidation. Because oxidative stress is closely linked to ischemic neuronal death, curcumin with its potent antioxidant property is anticipated to exert neuroprotective effects in our model.

Both the rate of cerebral perfusion and morphological integrity of the cerebral circulatory network play crucial roles for the physiological functioning of neurons and memory processes (1). A reduction in cerebral blood flow is implicated not only in vascular dementia but also in other types of dementia, such as AD (21). In the rat model of AD, two factors were proposed to be present before cognitive dysfunction and neurodegeneration is evident in the brain: advanced aging and a condition that decreases cerebral perfusion (5). Free radical generation, oxidative stress, and inflammation possibly contribute to the injury resulting from chronic cerebral hypoperfusion in animal models (2,5-7). Clinical findings also demonstrate that free radicals are able to mediate degeneration and death of neurons. Therefore, free radicals are likely associated with the pathogenesis of such neurodegenerative diseases as AD and vascular dementia (1,2). Oxygen free radicals are toxic to neurons, triggering chain reactions that result eventually in CNS injury (22). In the current study, whole brain tissue was used for measurements of MDA and GSH. This might be a pitfall for the study since dementia is involved with some areas of the brain (i.e. hippocampus). However, assuming that average amounts of MDA and GSH in the rest of the brain are in the same narrow range for each animal, whole brain would be safe for the measurements.

At menopause, circulating levels of estrogens decrease dramatically, influencing many brain processes that increase the prevalence of AD, stroke, and other forms of cerebrovascular diseases (9). There is some evidence that estrogen in CNS provides neuroprotection against various types of neurotoxicity in cellular and animal models (23). Functions of the brain were reported to be modulated by physiological variations in ovarian function. Thus, acute loss of ovarian hormones increases the fragility of neuron membranes. Furthermore, acute suppression of ovarian function possibly reduces activation of brain regions associated with memory (10,24). Therefore, the purpose of the current study was to evaluate whether long term administration of curcumin could attenuate oxidative stress and neuronal injury in chronic cerebral hypoperfusion of ovariectomized female rats. Our data showed that the tissue levels of GSH decreased while those of MDA increased in response to chronic cerebral hypoperfusion. Our results also showed that MDA content was markedly decreased and that GSH content significantly increased in the treatment group, suggesting curcumin may provide an efficient neuroprotection at least through attenuation of both oxidative stress and lipid peroxidation.

Neurons are very susceptible to ischemic events since oxidative metabolism and content of polyunsaturated fatty acids are high, whereas activities of antioxidant enzymes are relatively low in the CNS (25). In the present study, a significant increase in lipid peroxidation was observed as a result of free radical generation induced by chronic cerebral hypoperfusion. Furthermore, the concomitant decrease in GSH content was significant. Postischemic administration of curcumin remarkably reversed the tissue contents of MDA and GSH. Previous studies in the treatment of stroke show that curcumin exerts some beneficial effects through various processes, such as keeping intracellular Ca^{+2} at low levels, reducing nitric oxide-induced peroxynitrite and apoptosis (26), inhibiting lipid peroxidation (17), preventing endothelial cell damage in cerebral capillaries, alleviating vasogenic edema, and enhancing the stability of the blood-brain barrier (12). In addition, curcumin augments activities of such antioxidant enzymes as SOD, GSH, glutathione-s-transferase, catalase, and glutathione peroxidase (27). Moreover, Wu et al. (2006) reports that curcumin decreases oxidative stress in traumatic brain injury possibly via the BDNF system (28).

GSH is the most abundant non-protein thiol in the brain tissue (29). It is an endogenous antioxidant that participates in elimination of free radicals; thus, providing protection against oxidative stress (30). Therefore, the most important and significant alteration in antioxidant system is the decrease in GSH content. Depleted GSH or genetically deleted GSH peroxidase exacerbate the infarct size in transient focal ischemia which provides further evidence that preservation of GSH-mediated antioxidant defense is very important for cell survival (31). In the present study, chronic cerebral hypoperfusion decreased the GSH content in the brain tissue. However, treatment with curcumin reversed the disturbed level of GSH. Curcumin leveled off GSH content during chronic cerebral

hypoperfusion, an effect that may be related to its free radical scavenging action, thus minimizing the amount of these radicals, synergizing the enzymes and normalizing their activity. The data collected in the current study are consistent with those from previous studies in which treatment with curcumin increased GSH content, enhanced SOD activity, and lowered lipid peroxidation in both global and focal cerebral ischemia (14,17).

Besides oxidative stress, chronic cerebral hypoperfusion is also associated with reactive atrogliosis and activation of microglial cells (21,32). Reactive gliosis can produce excess amounts of cytokines, inflammatory products, and oxygen free radicals that exacerbate ischemic injury. Curcumin is reported to exert anti-inflammatory effect in many studies. This effect of curcumin is possibly mediated by its ability to inhibit cyclooxygenase-2 (COX-2), lipoxygenase (LOX), and inducible nitric oxide synthase (iNOS) (12,17,33). Moreover, it inhibits expression of proinflammatory cytokines by nuclear factor-kappa-Beta (12,34). Therefore, the anti-inflammatory effect of curcumin is assumed to contribute to the beneficial effects observed in the current study possibly through reducing the amount of free radicals released by leukocytes.

Many studies have focused on antioxidants for developing neuroprotective agents in treatment of stroke, which is an acute and progressive neurodegenerative disorder and the second leading cause of death in the world. Curcumin is able to cross the blood- brain barrier. Moreover, it potentially inhibits formation of amyloid beta oligomers and fibrils in mice (35). Therefore, curcumin has been recommended for clinical trials to prevent or treat AD and other types of neurodegenerative diseases. Results of the present study indicate that curcumin provides protection against oxidative stress and lipid peroxidation triggered by chronic cerebral hypoperfusion, which imitates vascular dementia. Thus, curcumin treatment appears to be a promising pharmacological agent to develop therapeutic approaches for prevention or treatment of cerebrovascular diseases such as vascular dementia, especially in women of advanced age and women experiencing menopause.

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