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Curcumin Ameliorates Cerebral Ischemia-induced Oxidative Stress by Modulating Lipid Peroxidation, Antioxidant Activity, Essential Elements, Transition, and Toxic Metals

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Abstract

Cerebral ischemic insult not only generates reactive oxygen species but increases oxidative stress and further cerebral injury. Curcumin is a natural polyphenol compound possesses antioxidant property. This study explored whether the neuroprotective mechanism of curcumin during cerebral ischemia is associated with the modulation of lipid peroxidation, the antioxidant superoxide dismutase (SOD), catalase (CAT), the essential element magnesium (Mg), zinc (Zn), selenium (Se), transition metal iron (Fe), copper (Cu), and toxic metal lead (Pb). Experimentally, a total of forty Sprague–Dawley male rats were used in the present study. Cerebral ischemia was induced by ligation of the right common carotid artery (RCCA) and the right middle cerebral artery (RMCA) for 1 hour. The prevention group was intraperitoneally injected with curcumin (100 mg/kg) once daily for consecutive 10 days before artery ligation. The right cerebral cortex was homogenized and the supernatants were harvested for biochemical analysis. Experimental results indicated that cerebral ischemic injury decreased SOD, CAT, Mg, Zn, Se, but increased MDA, Fe, Cu, and Pb. In turn, pretreating rats with curcumin before ischemic insult significantly reversed all biochemical results. Our findings suggest that curcumin attenuates cerebral ischemia-induced oxidative stress via modulating lipid peroxidation, antioxidant activity, essential elements, transition, and toxic metals. Crucially, the present results provide a new possibility for the therapeutic strategy of curcumin to chelate other neurotoxic metals. (J Intern Med Taiwan 2022; 33: 448-458)

Key Words: Cerebral ischemia, Curcumin, Lipid peroxidation, Transition metal, Essential element, Toxic metal

Introduction

Cerebral ischemia is the major leading cause of disability and death in aged population worldwide[1]. Ischemic stroke is caused by artery occlusion so as to interrupt blood flow into the affected brain tissues. Meanwhile, cerebral ischemic insult generates numerous toxic reactive oxygen species (ROS) including superoxide radicals, hydrogen peroxide, and hydroxyl radicals[2]. In this case, ROS-mediated

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deleterious lipid peroxidation and oxidative injury occur[1,2]. The principle of deleterious lipid peroxidation is that toxic ROS can spontaneously attack the component of polyunsaturated fatty acids (PUFA) on cells[1]. In fact, the brain is very vulnerable to ROS attack because of the following characteristics including higher PUFA component, high aerobic metabolism, and less antioxidant activity[2]. Hence, maintaining proper antioxidant capacity is helpful for protecting the brain against cerebral ischemia-induced ROS and further oxidative stress.

Curcumin is a natural polyphenol compound that exists in fruits and vegetables mainly for plants to protect against environmental stress[3,4]. Animal study has documented that curcumin displays broad beneficial properties such as free radical scavenge, anti-oxidation, anti-inflammation, and metal chelation[4,5]. As such, curcumin has been widely used in the treatment of numerous ROS-involved human diseases such as Alzheimer's disease, Parkinson's disease, type 2 diabetes mellitus, brain, kidney, and liver diseases [3-7].

The antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT) are pivotal for protecting brain tissues from ROS attack[8,9]. Detoxification by SOD occurs via converting toxic superoxide radicals into hydrogen peroxide, and the CAT then converts hydrogen peroxide into non-toxic water[8-10]. Thereby, maintaining proper antioxidant activity is beneficial to attenuate ROS and further oxidative stress and injury. In turn, decreased antioxidant activity not only represents elevated oxidative stress but also correlates with increased oxidative devastation[9,10].

Appropriate essential elements magnesium (Mg), zinc (Zn), and selenium (Se) are substantial for normal brain functions because these elements possess innate antioxidant capacity[1,2,8]. The transition metals iron (Fe) and copper (Cu) are required for the brain. However, overload can spontaneously generate harmful ROS via deleterious Fenton reaction, thus leading to increased oxidative stress and lipid peroxidation in the brain[11-16]. Toxic metal lead (Pb) is also recognized as a serious threat to human health and its toxicity is evidenced in correlation to ROS generation as well as antioxidant activity reduction[17-20]. Although extensive research exploring the mechanism underlying curcumin neuroprotection, whether this mechanism involves the regulation of brain concentrations of essential elements, transition, and toxic metals has not been investigated to date and is the purpose of this study.

Materials and Methods

Animal pretreatment, grouping, and cerebral ischemic surgery

In this study, a total of forty Sprague–Dawley male rats which body weight ranging from 200 to 250 g were purchased from BioLASCO (Taipei, Taiwan). In order to stabilize the physiological condition of the experimental animals, all rats were kept in stainless-steel mesh cages and housed under controlled conditions (22±2°C, 50±20% relative humidity, 12-h light-dark cycle) with diet and water for 7 days followed by randomly separated into four groups as below: control (1% DMSO was dissolved in 1 mL of normal saline followed by intraperitoneally given to the rats once daily for consecutive 10 days); ligation (rats were treated with 1% DMSO that was dissolved in 1 mL of normal saline and intraperitoneally given to the rats once daily for consecutive 10 days followed by occlusion of the right common carotid artery (RCCA) and right middle cerebral artery (RMCA) for 1 hour); curcumin (rats were intraperitoneally given with curcumin at the dosage of 100 mg/kg that was dissolved in 1% DMSO solution once daily for 10 days); and prevention (rats were pretreated with curcumin at the dosage of 100 mg/kg that was dissolved in 1% DMSO once daily for 10 days followed by occlusion the artery of RCCA and RMCA for 1 hour). All experimental rats were sacrificed and the fresh cerebral cortex samples were immediately harvested for

further biochemical analysis. In this experiment, all the experimental protocol throughout animal processing procedures was approved by the Institutional Animal Care and Use Committee of Central Taiwan University of Science and Technology (IACUC, 109-CTUST-002).

Malondialdehyde (MDA) concentration analysis in the cerebral cortex homogenates

In total of 0.2 g of the cerebral cortex samples were homogenized in the volume of 5 mL of ice KCl (154 mM) by Teflon pestles homogenizers, and the supernatants were harvested. Experimentally, 200 μL of the supernatant was mixed with 3 mL of the H_3PO_4 and 800 μL of the KCl solution followed by vortex well. The standard solution of 1, 1, 3, 3-tetra ethoxy propane was applied to interact with the thiobarbituric acid (TBA) substance and was boiled for 60 minutes. Finally, 4 mL of the butanol solution was added to the solution and vortex for 5 min followed by collecting the supernatant for MDA analysis. Basically, the detective principle of MDA is based on the measurement of the pink color that is generated through the reaction of MDA with TBA. The concentrations of MDA were determined by spectrophotometer at 532 nm (U-1900, Hitachi, Japan).

Analysis of antioxidant activity in the cerebral cortex homogenates

The SOD activity was detected according to the procedures of Cayman's superoxide dismutase assay kit which is purchased from Cayman Chemical Company (Ann Arbor, MI, USA). Briefly, xanthine oxidase can react with the hypoxanthine to generate the superoxide radical. The superoxide radical can reacted with tetrazolium salt and the SOD activity was measured by spectrophotometer (Thermo Scientific Multiskan Spectrum, Vantaa, Finland). On the other hand, the CAT activity was assayed by catalase commercial kit purchased from Cayman Chemical Company (Ann Arbor, MI, USA). Presently, the analytical procedure is that the methanol interacts with hydrogen peroxide under the catalysis of the CAT enzyme to produce the formaldehyde. Finally, the chromogen of 4-amino-3-hydrazino-5-mercapto-1,2, 4-triazole was reacted with the formaldehyde and the CAT activity was detected by spectrophotometry (Thermo Scientific Multiskan Spectrum, Vantaa, Finland).

Essential elements, transition, and toxic metals analysis in the cerebral cortex homogenates

To measure the concentration of Mg, Zn, Se, Fe, Cu, and Pb, 2 mL of ultrapure-grade nitric acid solution was used for wet-digestion with 0.2 g of the fresh cerebral cortex sample overnight. In this study, 50% nitric acid solution was well prepared for completely soaking all containers that were used to analyze the essential elements, transition, and toxic metals. The standard solutions of all analyzed metals were purchased from Merck (Darmstadt, Germany). The SavantAA Z graphite furnace atomic absorption spectrophotometer (GBC Scientific Equipment, Braeside, Australia) with longitudinal Zeeman Effect background correction and PAL4000 autosampler system was used in the present experiment.

Protein level measurement in the cerebral cortex homogenates

For protein analysis, the commercial kit of Bio-Chain protein assay (San Francisco, CA, USA) was used in this present work. In brief, the analytical principle of this protein assay kit was improved by the Protein assay method of Coomassie Blue G. In general, the analytical principle is that the reagent interacted with the protein to produce a blue color complex and its color intensity is proportional to protein concentration. The protein concentration was assayed by spectrophotometry (Thermo Scientific Multiskan Spectrum, Vantaa, Finland) at the wavelength of 595 nm experimentally.

Statistical analysis of the experimental data

All the obtained data were statistically expressed as mean ± S.D. The experimental data were measured by the statistical method of Kruskal–Wallis one-way analysis of variance (ANOVA). If the data exhibit significant differences among groups, the Fisher's Least Significant Difference (FLSD) method was applied to compare each group. Once the p-value was less than 0.05, the statistical differences were considered significantly in the present work. a: $p < 0.05$, vs. control; b: $p < 0.05$, vs. ligation.

Results

Regarding the MDA concentration, a significant ($p < 0.05$) reduction of the MDA level was found in the group of prevention as compared to the ligation (Figure 1). In turn, the MDA level was statistically ($p < 0.05$) increased in the ligation group but decreased in the curcumin treatment group as compared to the control.

Figure 2 illustrates the profiles of the antioxidant activity of SOD and CAT in the homogenates of cerebral cortex. Compared to the ligation group, the

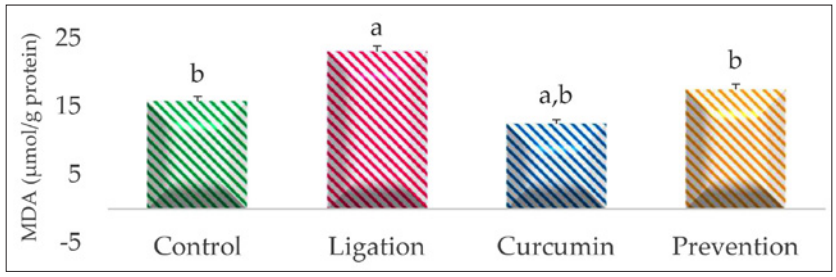

Figure 1. The malondialdehyde (MDA) levels in the right cerebral cortex homogenates. Data were expressed as mean ± S.D. The Kruskal–Wallis one-way analysis of variance (ANOVA) and the Fisher's Least Significant Difference (FLSD) test were used. The difference was considered significant at $P < 0.05$. a: $P < 0.05$ vs. control group; b: $P < 0.05$ vs. ligation group.

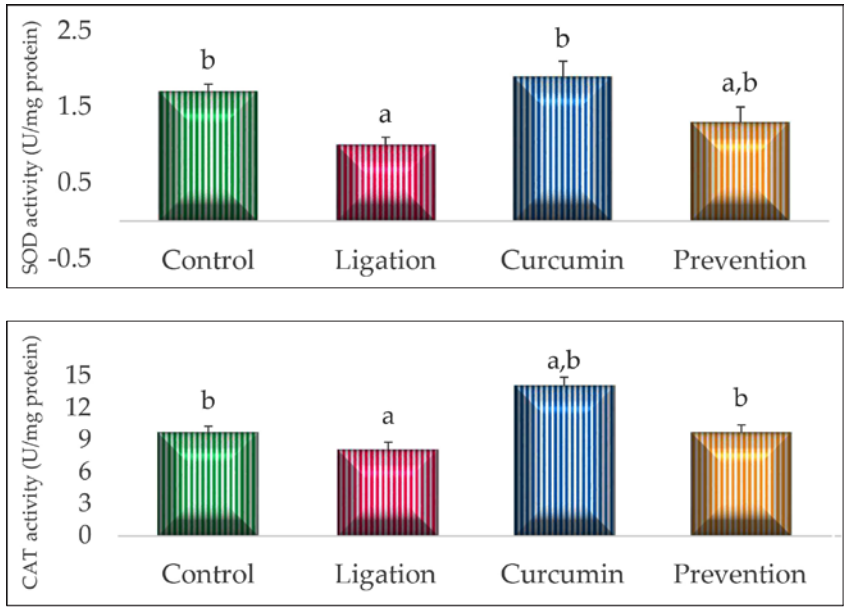

Figure 2. The antioxidant activity of SOD (upper histogram) and CAT (lower histogram) in the right cerebral cortex homogenates. The obtained data were expressed as mean ± S.D. See Figure 1 for the statistical methods. The statistical difference was considered significant at $P < 0.05$. a: $P < 0.05$ vs. control group; b: $P < 0.05$ vs. ligation group.

SOD activity was significantly ($p < 0.05$) increased in the group of control, curcumin, and prevention. Meanwhile, the SOD activity was markedly ($p < 0.05$) declined in ligation and prevention group as compared to the control group. The CAT activity was obviously ($p < 0.05$) enhanced in the group of control, curcumin, and prevention as compared to the ligation. On the other side, the CAT activity was obviously ($p < 0.05$) decreased in the group of ligation but increased in the curcumin as compared to the control group.

The data given in Figure 3 showed the profiles of the essential element Mg, Zn, and Se in the cerebral cortex homogenates. The Mg level was statistically ($p < 0.05$) elevated in the group of control, curcumin, and prevention as compared to the ligation. On the contrary, the Mg level was markedly declined ($p < 0.05$) in the group of ligation as compared to the control. The Zn concentration in the cerebral cortex was markedly ($p < 0.05$) increased in the group of control, curcumin, and prevention as compared to the artery ligation group. In contrast, the Zn level was significantly ($p < 0.05$) decreased in the group of ligation as compared to the control. Likewise, the Se concentration was obviously ($p < 0.05$) elevated in the group of control, curcumin as well as prevention as compared to the ligation. Compared to the control group, the level of essential element Se was markedly declined ($p < 0.05$) in the group of ligation but increased in the curcumin.

The present results demonstrate that a significant ($p < 0.05$) decrease of the Fe level was found in the group of control, curcumin, and prevention

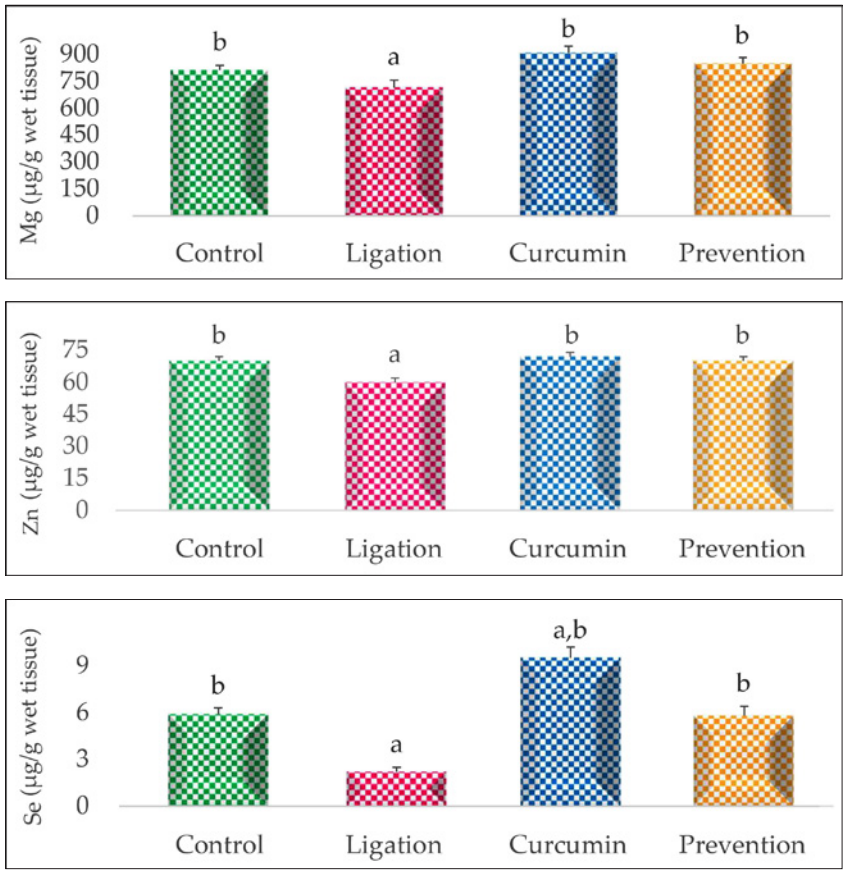

Figure 3. The essential element levels of magnesium (Mg; upper histogram), zinc (Zn; middle histogram), and selenium (Se; lower histogram) in the right cerebral cortex homogenates. All data were expressed as mean ± S.D. See Figure 1 for the statistical methods. The statistical difference was considered significant at $P < 0.05$. a: $P < 0.05$ vs. control group; b: $P < 0.05$ vs. ligation group.

as compared to the ligation (Figure 4). Conversely, the Fe level was markedly ($p < 0.05$) increased in the group of ligation as compared to the control. By comparison with the ligation group, the Cu level was statistically ($p < 0.05$) declined in the group of control, curcumin, and prevention. In turn, the Cu concentration was statistically increased ($p < 0.05$) in the group of ligation as compared to the control group. Results indicate that curcumin can effectively reduce both transition metal levels.

Finally, there is a statistically significant decrease ($p < 0.05$) in the concentration of Pb observed in the group of control, curcumin, and prevention as compared to the ligation (Figure 5). Conversely, the Pb level was obviously increased ($p < 0.05$) in the group of ligation but decreased in the group of curcumin as compared to the control. The present result reinforces that curcumin can effectively decrease the toxic metal Pb.

Discussion

Our experimental findings suggest that cerebral ischemia results in brain tissue decreases in the level of Mg, Zn, Se, SOD, CAT, and increases in the concentrations of MDA, Fe, Cu, and Pb in the ischemic cerebral cortex. Interestingly, pre-

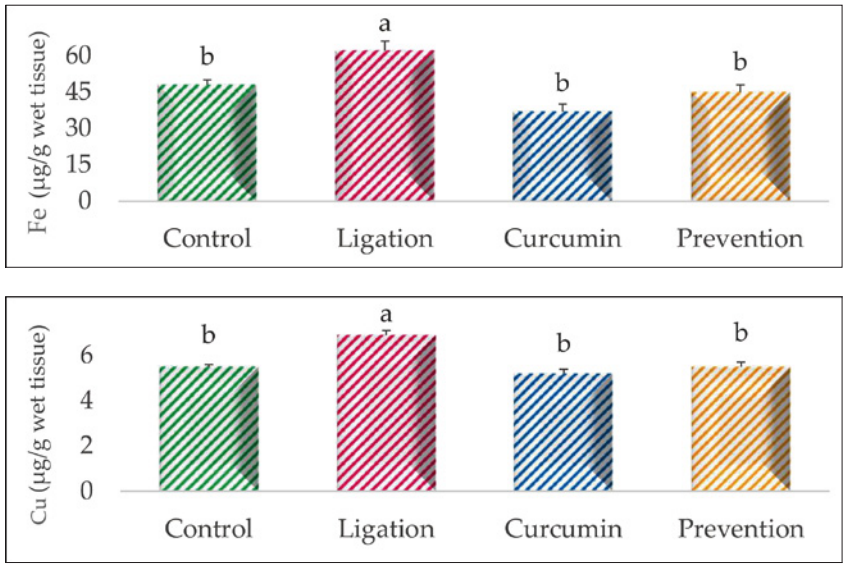

Figure 4. The transition metal concentrations of iron (Fe; upper histogram) and copper (Cu; lower histogram) in the right cerebral cortex homogenates. All data were expressed as mean ± S.D. See Figure 1 for the statistical methods. The statistical difference was considered significant at $P < 0.05$. a: $P < 0.05$ vs. control group; b: $P < 0.05$ vs. ligation group.

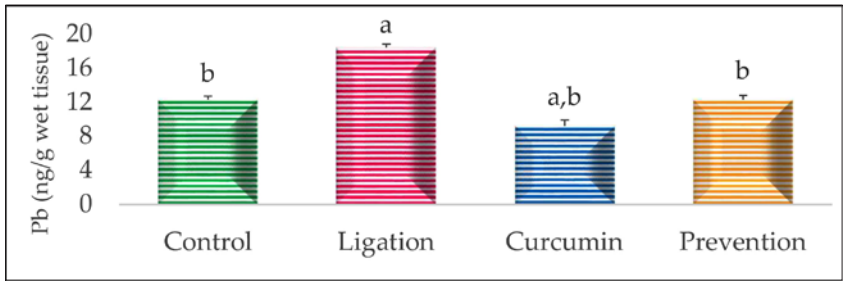

Figure 5. The toxic metal concentrations of lead (Pb) in the right cerebral cortex homogenates. Data were expressed as mean ± S.D. See Figure 1 for the statistical methods. The statistical difference was considered significant at $P < 0.05$. a: $P < 0.05$ vs. control group; b: $P < 0.05$ vs. ligation group.

treating rats with curcumin before ischemic injury statistically reversed all experimental results. The previous investigation indicates that curcumin possesses beneficial effects on humans and animals due to its beneficial properties of anti-oxidation and anti-inflammation[3]. It is reported that polyphenol compound curcumin provides neuroprotection by attenuating multiple sclerosis devastation through down-regulating inflammation, oxidative processes, and enhancing myelin repair[4,21]. In addition, curcumin protects against amyloid β-induced mitochondrial and synaptic toxicities by reducing ROS-mediated lipid peroxidation in Alzheimer's disease[22]. Animal research reveals that curcumin is capable to alleviate cerebral ischemia and reperfusion devastation via reducing ROS and further ROS-induced lipid peroxidation in rats with spinal cord injury[23]. Furthermore, a clinical study indicates the beneficial effect that curcumin supplementation not only increases the brachial artery blood flow but also reduces inflammation and oxidative stress in healthy middle-aged and older adults[24].

Cerebral ischemia is characterized by cerebral artery occlusion so as to interrupt the blood flow into the affected brain tissues [1]. Ischemic stroke is attended with increased oxidative stress resulting from uncontrolled ROS generation[2]. The preceding study demonstrates that ROS generation results from ischemic stroke markedly increases lipid peroxidation in the affected brain[8]. In fact, polyunsaturated fatty acid (PUFA) is the major constituent of the brain and is the primary target of ROS attack because of its double-bond structure[9]. Cerebral ischemic insult-generated ROS can as a result enhance lipid peroxidation and oxidative stress in the affected brain. Our present finding supports the previous observation and reveals that curcumin performs antioxidant capacity to scavenge ischemic injury-generated ROS and to attenuate oxidative stress as reflected by a decreased MDA concentration[1,2,8,9]. In addition to this, lower antioxidant capacity makes the brain highly susceptible to ROS attack [8-10]. The present findings demonstrate that ischemic stroke decreases SOD and CAT activities but curcumin markedly enhances both enzyme activities. *In vivo* and *in vitro* studies propose that curcumin is capable of up-regulating the activity of SOD and CAT[3-5], demonstrating that increased SOD and CAT activities are useful to decline further ROS-mediated lipid peroxidation and oxidative stress.

Although numerous achievements over the years in investigating the mechanisms of curcumin underlying neuroprotection concerns to inhibit NF-kB mediated transcription, inflammatory cytokines, and induce iNOS and Cox-2 resulting in its antioxidant and anti-inflammatory properties, it has not yet been explored whether the neuroprotective mechanism of curcumin is associated with the modulation of the transition metal, essential elements as well as toxic metals. Previous study reveals that perturbation of essential elements is the first step in initiating the processes of brain cell death[9]. Therefore, realizing the association between the alteration of essential element levels and cerebral ischemic injury is advantageous for insight into the pathophysiology of the ischemic stroke. It has been evidenced that Mg is the most abundant intracellular cations and involves pleiotropic functions such as protecting cells from oxidative attack, ameliorating inflammatory response, modulating energy metabolism, regulating ATP synthesis, reducing neuronal excite-toxicity, and acting as a calcium blocker[1,8,9]. In this study, ischemic stroke results in a decreased Mg level but pretreating rats with curcumin before ischemia significantly enhances the Mg concentration. Clearly, our finding indicates that curcumin is capable of enhancing the Mg level. As noted above, numerous positive effects of Mg have been reported, including reducing oxidative stress, stabilizing cell membrane functions, increasing cerebral blood flow, modulating energy metabolism and ATP synthesis[1,2,8,9]. Study indicates curcumin can obviously

increase artery blood flow in healthy middle-aged and older adults[24]. This may be explained noting that enhanced cerebral blood flow may enhance the Mg level; increased Mg is useful to promote energy metabolism as well as ATP synthesis. As a result, better energy supplementation is helpful to attenuate cerebral ischemia-induced oxidative stress and lipid peroxidation. Essential element Zn involves numerous biological functions mainly in anti-oxidation and anti-inflammation[1]. Our preceding study evidenced that cerebral ischemia decreases Zn but increases the MDA level[1]. Besides, previous study suggests that an inverse association between Zn and MDA levels is found in the ischemic cerebral cortex[2,8]. In this study, ischemic insult decreases Zn but increases the MDA levels. However, pretreating rats with curcumin before ischemic injury markedly enhances the Zn concentration but decreases the MDA levels. It is of note that curcumin is able to enhance the Zn level; in this situation, Zn performs its innate antioxidant ability so as to attenuate ROS-mediated lipid peroxidation injury in the ischemic cerebral cortex. Likewise, the essential element Se is reported to display excellent antioxidant ability in eliminating ROS as well as lipid peroxidation devastation[2,8,9]. Clinical study demonstrates a negative correlation between the serum Se level and the occurrence of acute ischemic stroke[25]. Animal study suggests that pretreating Alzheimer's disease model rats with sodium selenate markedly decreases neurological deficits[26]. Furthermore, supplementation of Se to lymphocytes collected from patients with Alzheimer's disease markedly reduces ROS levels and ROS-mediated lipid peroxidation devastation[27]. In this study, pretreating rats with curcumin before ischemia obviously enhanced Se levels but decreased the MDA concentration. Based on our finding, we suggest that curcumin treatment is helpful to enhance the blood flow and Se levels. Thus, Se exerts its innate antioxidant capacity so as to attenuate cerebral ischemia-generated ROS and further ROS-mediated lipid peroxidation. Taken together, curcumin supplementation improves cerebral blood flow in the ischemic cerebral cortex; under this circumstance, levels of essential element Mg, Zn, and Se are increased and consequently, these elements exert its innate antioxidant property to effectively eliminate cerebral ischemia-induced ROS. Given this fact, lipid peroxidation and oxidative stress are ameliorated.

The transition metal Fe and Cu is required for living organisms because they involved in a variety of biological functions[14,15]. However, Fe and Cu overload is toxic to cells because they initiate deleterious Fenton reactions, generating toxic hydroxyl radicals and leading further oxidative injury in cells [11-13,16]. The previous study demonstrates that owing to the interruption of the blood flow, cerebral ischemic insult not only results in less energy supplementation but reduces Fe and Cu metabolism. As a result, Fe and Cu are overloaded in the affected brain[1,2,9]. On the other hand, cerebral ischemic injury-generated hydrogen peroxide (H_2O_2) can actively react with Fe and Cu, thus generating toxic hydroxyl radicals via deleterious Fenton reaction and resulting in further oxidative devastation[10,16]. In fact, the polyphenol compound curcumin has gained much attraction concerning its metal chelating property[3-7,18]. The present study indicates that pretreating rats with curcumin before ischemic insult significantly decreases Fe and Cu levels. Obviously, the finding of this experiment is consistent with the previous investigation, indicating that curcumin can effectively chelate the transition metals Fe and Cu. Under this situation, declined Fe and Cu levels are beneficial not only to alleviate the Fenton reaction-generated ROS but to ameliorate further ROS-mediated lipid peroxidation and oxidative stress.

The toxic metal lead (Pb) presents as a contaminant in the environment worldwide[2,8]. In fact, Pb does not implicate any biological functions in living organisms and notably, once the toxic

metal Pb enters the body, it accumulates in numerous organs, especially in the brain so as to result in neurotoxicity[9,10]. Previous studies evidence that the toxic mechanism underlying Pb neurotoxicity is due to ROS generation as well as antioxidant capacity reduction[8,17,18]. Studies reveal that based on its chemical structure, the polyphenol compound such as resveratrol can effectively chelate Pb so as to decline Pb-induced cerebral cortex injury in animal model[17,18]. Likewise, the present finding suggests that cerebral ischemia results in Pb overload but this adverse phenomenon can be reversed by pretreatment rats with curcumin before ischemic injury. As already mentioned, the polyphenol structure possesses innate chelating properties. In light of this effect, we suggest that polyphenol compound curcumin is capable of exerting chelating capacity so as to significantly chelate the toxic metal Pb in the ischemic cerebral cortex. In this situation, further Pb-generated ROS and ROS-induced lipid peroxidation and oxidative stress are mitigated.

Conclusion

Our experimental findings reveal that the emerging role of the polyphenol compound curcumin confers neuroprotection to effectively alleviate cerebral ischemia-induced oxidative stress. The previous study demonstrate that chelating agent possesses the properties of high affinity to the transition and toxic metals but low affinity to the essential elements[2]. This is the first paper demonstrating that the neuroprotection of curcumin is associated with the ionic mechanism that correlates with the modulation of essential elements, transition metals, and toxic metals. In addition, it is notable that the present findings provide a new possibility for the therapeutic strategy of curcumin in chelating other neurotoxic metals.

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Conflicts of Interest

The authors declare no conflict of interest.

Declaration

This research paper has not been published elsewhere.

References

1. Fang KM, Cheng FC, Huang YL, et al. Trace element, antioxidant activity, and lipid peroxidation levels in brain cortex of gerbils after cerebral ischemic injury. Biol Trace Elem Res 2013;152(1):66-74. doi: 10.1007/s12011-012-9596-1. Epub 2013 Jan 19. PMID: 23334863.
2. Ro JH, Liu, CC, Lin, MC. Resveratrol mitigates cerebral ischemic injury by altering levels of trace elements, toxic metal, lipid peroxidation, and antioxidant activity. Biol Trace Elem Res 2021;199, 3718-3727. https://doi.org/10.1007/s12011-020-02497-x.
3. Reddy PH, Manczak M, Yin X, et al. Protective effects of a natural product, curcumin, against amyloid β induced mitochondrial and synaptic toxicities in Alzheimer's disease. J Invest Med 2016;64(8):1220-34. doi:10.1136/jim-2016-000240.
4. Benameur T, Giacomucci G, Panaro MA, et al. New promising therapeutic avenues of curcumin in brain diseases. Molecules 2021;27(1):236. Published 2021 Dec 31. doi:10.3390/molecules27010236.
5. Panahi Y, Khalili N,; Sahebi, E, et al. Antioxidant effects of curcuminoids in patients with type 2 diabetes mellitus: A randomized controlled trial. Inflammopharmacology 2017; 25:25-31. [CrossRef] [PubMed].
6. Saeidinia A, Keihanian F, Butler AE, et al. Curcumin in heart failure: A choice for complementary therapy? Pharmacol Res 2018;131:112-19. [CrossRef] [PubMed].
7. Samarghandian S, Azimi-Nezhad M, Farkhondeh T, Samini F. Anti-oxidative effects of curcumin on immobilization-induced oxidative stress in rat brain, liver and kidney. Biomed Pharmacother. 2017;87:223-229. doi:10.1016/j.biopha.2016.12.105.
8. Lin MC, Liu CC, Lin YC, et.al. Epigallocatechin gallate modulates essential elements, Zn/Cu ratio, hazardous metal, lipid peroxidation, and antioxidant activity in the brain cortex during cerebral ischemia. Antioxidants 2022;11(2):396. Published 2022 Feb 16. doi:10.3390/antiox11020396.
9. Lin MC, Liu CC, Liao CS, et.al. Neuroprotective effect of quercetin during cerebral ischemic injury involves regulation of essential elements, transition metals, Cu/Zn ratio, and antioxidant activity. Molecules 2021;26(20):6128. Published 2021 Oct 11. doi:10.3390/molecules26206128.

10. Lin MC, Liu CC, Lin YC, et.al. Resveratrol protects against cerebral ischemic injury via restraining lipid peroxidation, transition elements, and toxic metal levels, but enhancing anti-oxidant activity. Antioxidant 2021;10(10):1515. Published 2021 Sep 24. doi:10.3390/antiox10101515.
11. Allen KJ, Gurrin LC, Constantine CC, et.al. Iron-overload-related disease in HFE hereditary hemochromatosis. N Engl J Med 2008;358:221-30. [CrossRef].
12. Murphy CJ, Oudit GY. Iron-overload cardiomyopathy: Pathophysiology, diagnosis, and treatment. J Card Fail 2010; 16:888-900. [CrossRef].
13. Matos, Gouveia AM, Almeida H. Resveratrol attenuates copper-induced senescence by improving cellular proteostasis. Oxid Med Cell Longev 2017;3793817. [PubMed].
14. Jomova K, Valko M. Advances in metal-induced oxidative stress and human disease. Toxicology 2011; 283: 65-87. [CrossRef].
15. Jaishankar M, Tseten T, Anbalagan N, et.al. Toxicity, mechanism and health effects of some heavy metals. Interdiscip Toxicol 2014;7:60-72. [CrossRef].
16. Valko M, Jomova K, Rhodes CJ, et.al. Redox-and non-redox-metal-induced formation of free radicals and their role in human disease. Arch Toxicol 2016;90:1-37. [CrossRef].
17. Ding Y, Gonick HC, Vaziri ND. Lead promotes hydroxyl radical generation and lipid peroxidation in cultured aortic endothelial cells. Am J Hypertens 2000;13:552-55. https://doi.org/10.1016/ s0895-7061(99)00226-5.
18. Flora SJS, Mittal M, Mehta A. Heavy metal induced oxidative stress& its possible reversal by chelation therapy. Indian J Med Res 2008; 128:501-23.
19. Saxena G, Flora SJS. Changes in brain biogenic amines and haembiosynthesis and their response to combined administration of succimers and Centella asiatica in lead poisoned rats. J Pharm Pharmacol 2006;58:547-59. https://doi.org/10.1211/jpp.58.4.0015.
20. Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. Oxidative Med Cell Longev 2009;2:270-78.
21. Mohajeri M, Sadeghizadeh M, Najafi F, et.al. Polymerized nano-curcumin attenuates neurological symptoms in EAE model of multiple sclerosis through down regulation of inflammatory and oxidative processes and enhancing neuroprotection and myelin repair. Neuropharmacology 2015;99:156-67. [CrossRef].
22. He R, Jiang Y, Shi Y,et.al. Curcumin-laden exosomes target ischemic brain tissue and alleviate cerebral ischemia/reperfusion injury by inhibiting ROS-mediated mitochondrial apoptosis. Mater Sci Eng C Mater Biol 2020;117:111314. [CrossRef] [PubMed].
23. Fakhri S, Abbaszadeh F, Moradi SZ,et.al. Effects of polyphenols on oxidative stress, inflammation, and interconnected pathways during spinal cord injury. Oxid Med Cell Longev 2022;8100195. Published 2022 Jan 7. doi:10.1155/2022/8100195.
24. Santos-Parker, J. R., Strahler, T. R., Bassett, C. J., Bispham, N. Z., Chonchol, M. B., & Seals, D. R. Curcumin supplementation improves vascular endothelial function in healthy middle-aged and older adults by increasing nitric oxide bioavailability and reducing oxidative stress. Aging 2017;9(1): 187-205. https://doi.org/10.18632/aging.101149
25. Mirończuk A, Kapica-Topczewska K, Socha K, et.al. Selenium, copper, zinc concentrations and Cu/Zn, Cu/Se molar ratios in the serum of patients with acute ischemic stroke in northeastern Poland-A aew insight into stroke pathophysiology. Nutrients 2021;13:2139.
26. Van EerselJ, Ke YD, Liu X, et.al. Sodium selenate mitigates tau pathology, neurodegeneration, and functional deficits in Alzheimer's disease models. Proc Natl Acad Sci 2010;107: 13888-93.
27. Cosín-Tomàs M, Senserrich J, Arumí-Planas M, et.al. Role of resveratrol and selenium on oxidative stress and expression of antioxidant and anti-aging genes in immortalized lymphocytes from Alzheimer's disease patients. Nutrients 2019;11:1764.

薑黃素通過調節脂質過氧化、抗氧化活性、必需元素、過渡金屬和有毒金屬來改善腦缺血引起的氧化壓力

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摘 要

腦缺血損傷會產生活性氧並導致進一步的氧化壓力與腦損傷。薑黃素是一種天然多酚化合物，具有抗氧化特性。本研究探討薑黃素在腦缺血期間的神經保護機制是否與調節脂質過氧化作用(MDA)、抗氧化物超氧化物歧化酶(SOD)、過氧化氫酶(CAT)、必需元素鎂(Mg)、鋅(Zn)、硒(Se)、過渡金屬鐵(Fe)、銅(Cu)和有毒金屬鉛(Pb)有關。本研究總共使用了40隻雄性的Sprague-Dawley大白鼠。腦缺血係透過結紮右側頸總動脈和右側中腦動脈1小時來達成。預防組則於動脈結紮前先行每日1次腹腔注射薑黃素(100 mg/kg)且連續10天。隨後再將大腦皮質均質化後，收集上清液進行生化分析。實驗結果顯示：腦缺血損傷導致SOD、CAT、Mg、Zn和Se濃度降低但MDA、Fe、Cu與Pb濃度卻升高。相反的，在腦缺血損傷之前用薑黃素預先處理則顯著逆轉了所有生化結果。我們的研究結果顯示：薑黃素通過調節脂質過氧化、抗氧化活性、必需元素、過渡金屬和有毒金屬來改善腦缺血引起的氧化壓力。重要的是，本研究結果為薑黃素螯合其它神經毒性金屬的治療策略提供了新的可能性。