

Neuroprotective effects of tetrandrine against vascular dementia

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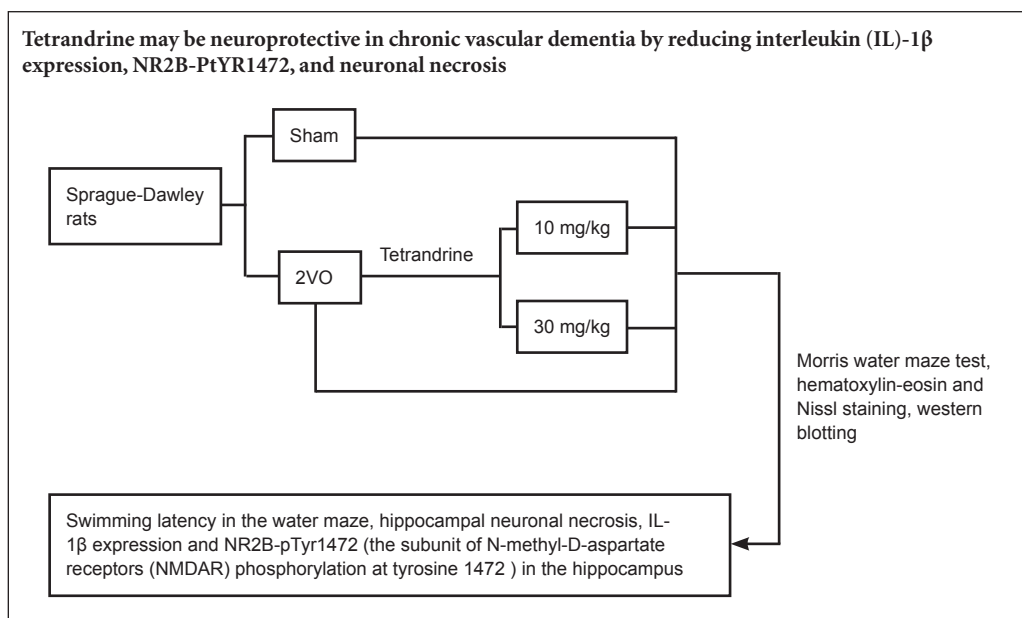
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Graphical Abstract



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Abstract

Tetrandrine is one of the major active ingredients in Menispermaceae *Stephania tetrandra* S. Moore, and has specific therapeutic effects in ischemic cerebrovascular disease. Its use in vascular dementia has not been studied fully. Here, we investigated whether tetrandrine would improve behavioral and cellular impairments in a two-vessel occlusion rat model of chronic vascular dementia. Eight weeks after model establishment, rats were injected intraperitoneally with 10 or 30 mg/kg tetrandrine every other day for 4 weeks. Behavioral assessment in the Morris water maze showed that model rats had longer escape latencies in training trials, and spent less time swimming in the target quadrant in probe trials, than sham-operated rats. However, rats that had received tetrandrine showed shorter escape latencies and longer target quadrant swimming time than untreated model rats. Hematoxylin-eosin and Nissl staining revealed less neuronal necrosis and pathological damage, and more living cells, in the hippocampus of rats treated with tetrandrine than in untreated model rats. Western blot assay showed that interleukin-1 β expression, and phosphorylation of the N-methyl-D-aspartate 2B receptor at tyrosine 1472, were lower in model rats that received tetrandrine than in those that did not. The present findings suggest that tetrandrine may be neuroprotective in chronic vascular dementia by reducing interleukin-1 β expression, N-methyl-D-aspartate receptor 2B phosphorylation at tyrosine 1472, and neuronal necrosis.

Key Words: nerve regeneration; tetrandrine; ischemic cerebrovascular disease; vascular dementia; N-methyl-D-aspartic acid receptor 2B; N-methyl-D-aspartate receptor 2B phosphorylation at tyrosine 1472; interleukin-1 β ; neuronal necrosis; neural regeneration

Introduction

Patients with vascular dementia often present with impairments in cognition, linguistic ability and memory (Doruk et al., 2010; Jiwa et al., 2010; Loganathan et al., 2010). Tyrosine phosphorylation of the N-methyl-D-aspartate receptor (NMDAR) has been implicated in nerve cell loss, developmental problems, cancers and ischemic brain injury (Manzerra et al., 2001; Haughey and Mattson, 2002; Viviani et al., 2006). Inflammatory cytokines modulate several neurological functions (Moghaddam et al., 2015; Pang et al., 2015; Yang et al., 2015). Recent studies have shown that the cytokine interleukin (IL)-1 β regulates various classic neurotransmitter systems (Balosso et al., 2008; Paul and Kang, 2013; Cassol et al., 2014; Kählin et al., 2014) and enhances NMDAR functions (Viviani et al., 2006). Recombinant IL-1 β potentiates neuronal death induced by NMDAR activation in primary hippocampal neurons, and increases phosphorylation of NMDAR subtype 2B (NR2B) at tyrosine 1472 (pTyr1472) (Viviani et al., 2003, 2006). Therefore, hypophosphorylation of NR2B may provide a mechanistic explanation for vascular dementia, and be a potential therapeutic target.

Tetrandrine (Tet) is a major active ingredient in Menispermaceae *Stephania tetrandra* S. Moore (Wang et al., 2004). Numerous studies support the notion that Tet is a potential therapeutic candidate against cancer (Shi et al., 2015; Wu et al., 2015), inflammation (Chen, 2002) and brain ischemia/reperfusion injury (Liu et al., 2001). Additionally, Tet can protect the liver, heart, small bowel and brain from ischemia/reperfusion injury (Chen et al., 2011). Tet is a calcium channel blocker, and can inhibit destructive factors in ischemia/reperfusion injury, such as lipid peroxidation, generation of reactive oxygen species, production of cytokines and inflammatory mediators, neutrophil recruitment and platelet aggregation (Chen et al., 2011). Therefore, Tet has potential as a protective agent in ischemic cerebrovascular disease. In the present study, we established an animal model of vascular dementia to explore the association of IL-1 β and NR2B phosphorylation, and investigated the molecular mechanism underlying the therapeutic effects of Tet against dementia in terms of NR2B phosphorylation.

Materials and Methods

Animals

A total of 40 specific-pathogen-free male Sprague-Dawley rats, aged 4 weeks and weighing 200 ± 10 g, were obtained from the Experimental Animal Center of Chongqing Medical University, China (certificate No. SCXK (Yu) 2012-0001). Rats were housed under a 12 hour light/dark cycle (lights on from 7:30 a.m.) at $24 \pm 1^\circ\text{C}$ and $55 \pm 5\%$ relative humidity. Food, vitamin supplements and distilled water were available throughout the light/dark cycle. The protocol was approved by the Animal Care Committee of the First Affiliated Hospital of Chongqing Medical University, China. The rats were equally and randomly divided into four groups: sham, two-vessel occlusion (2VO), 10 mg/kg Tet, and 30 mg/kg Tet.

Establishment of vascular dementia model by 2VO

Rats were anesthetized with 10% chloral hydrate (0.8

mL/200 g). The 2VO surgery was carried out as described previously (Baune et al., 2008). Briefly, a ventral median incision was made to expose the common carotid arteries, which were then separated from adjacent vessels and nerves, and occluded with No. 1 thread. The procedure for the sham-operated rats was identical except that the arteries were not occluded. After 7 days of recovery, animals were housed separately.

Drug administration

In the Tet groups, Tet (Mansite Pharmaceutical Co., Ltd., Chengdu, China; powder, purity > 98%, CAS No. 518-34-3; solvent, double-distilled water) was administered intraperitoneally (10 mg/kg or 30 mg/kg) once every other day for 4 weeks, from the eighth week after surgery (Liu et al., 2001).

Morris water maze

After 4 weeks of Tet administration, the Morris water maze task was conducted for 5 consecutive days. The time taken to climb onto the hidden platform was defined as the escape latency. Rats performed four training trials per day, with entry from each of the four quadrants. When the platform was found within 120 seconds, the rat was allowed to remain there for 20 seconds; if the rat failed to find the hidden platform within 120 seconds, it was placed on it and allowed to remain there for 20 seconds. The mean swimming time in the four quadrants was used to assess the learning and memory ability of the rats. Each day, following the final training trial, the platform was removed. The rats were released at the farthest position from where the platform had been, and allowed to swim for 60 seconds. The time spent in the target quadrant was recorded to evaluate cognitive performance (Xiong et al., 2006). Swimming was monitored by a video camera linked to a computer-based image analyzer (SLY-WMS Morris Water Maze System; Zhenghua Biological Equipment Co., Ltd., Huaibei, Anhui Province, China).

Histopathological observation

After the final behavioral test, three randomly selected rats in each group were perfused transcardially with PBS followed by cold 4% paraformaldehyde (Kinoshita et al., 1991; Mehraein et al., 2011; Chen et al., 2014). The brains were removed, embedded in paraffin, sectioned and processed for hematoxylin-eosin and Nissl staining. Serial coronal sections (5 μm thick) were taken at the level of the hippocampus and cerebral cortex. Nissl bodies appeared purple-blue and allowed identification of the basic neuronal structure (Shang et al., 2006). Photographs of the hippocampal CA1 region were taken using a camera (SX30 IS; Canon, Tokyo, Japan) attached to a microscope (BX51; Olympus, Beijing, China). Healthy neurons in the center of the CA1 region, showing clear boundaries without cellular shrinkage or cytoplasmic disintegration (Liu et al., 2007), were counted using Image Pro Plus 6.0 (Media Cybernetics Co., Silver Spring, MD, USA) in five randomly selected fields at 200 \times magnification, and the mean taken.

Western blot assay

IL-1 β , NR2B and NR2B-pTyr1472 protein expression in the hippocampus was evaluated by western blot assay. The total

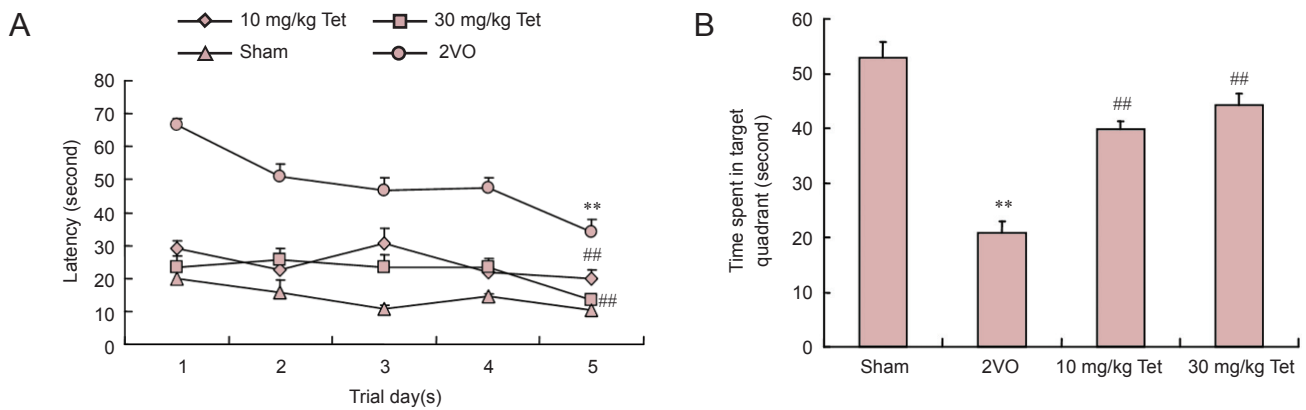


Figure 1 Effects of Tet on Morris water maze performance in rat models of vascular dementia. (A) Mean latency to find the hidden platform. (B) Swimming time in target quadrant after removal of platform (cut-off time, 60 seconds). Data are the mean \pm SD ($n = 10$ rats per group). ** $P < 0.01$, vs. sham group; ### $P < 0.01$, vs. 2VO group (one-way analysis of variance and Bonferroni *post hoc* test). Tet: Tetrandrine; 2VO: two-vessel occlusion.

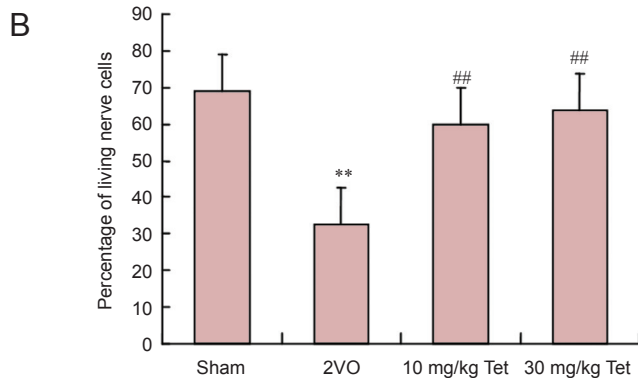
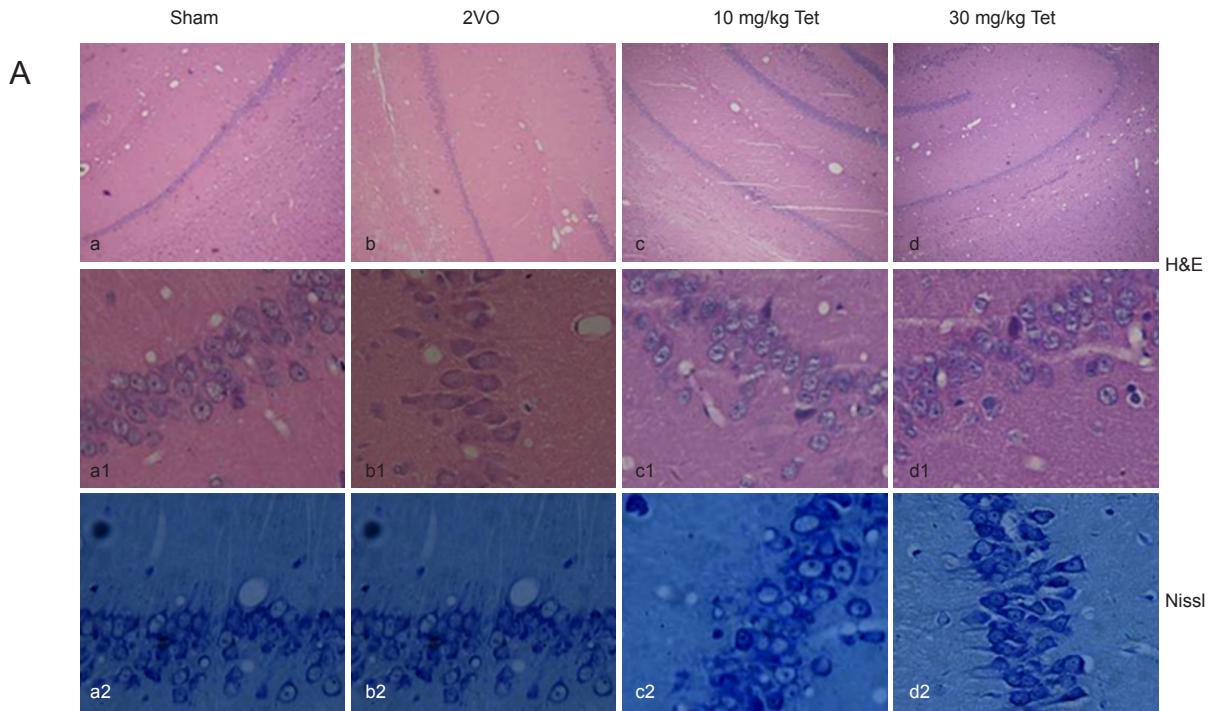


Figure 2 Effect of Tet on hippocampal CA1 pathology in rat models of vascular dementia. (A) H&E (upper panel, 40 \times magnification; middle panel, 200 \times magnification) and Nissl staining (lower panel, 200 \times magnification) of hippocampal CA1 showing atrophic or dying cells (arrows). Scale bars: Upper panel, 5 μ m; middle and lower panels, 50 μ m. (B) Percentage of living cells in CA1 (mean \pm SD, $n = 3$ rats per group). ** $P < 0.01$, vs. sham group; ### $P < 0.01$, vs. 2VO group (one-way analysis of variance and Bonferroni *post hoc* test). Tet: Tetrandrine; 2VO: two-vessel occlusion; H&E: hematoxylin-eosin.

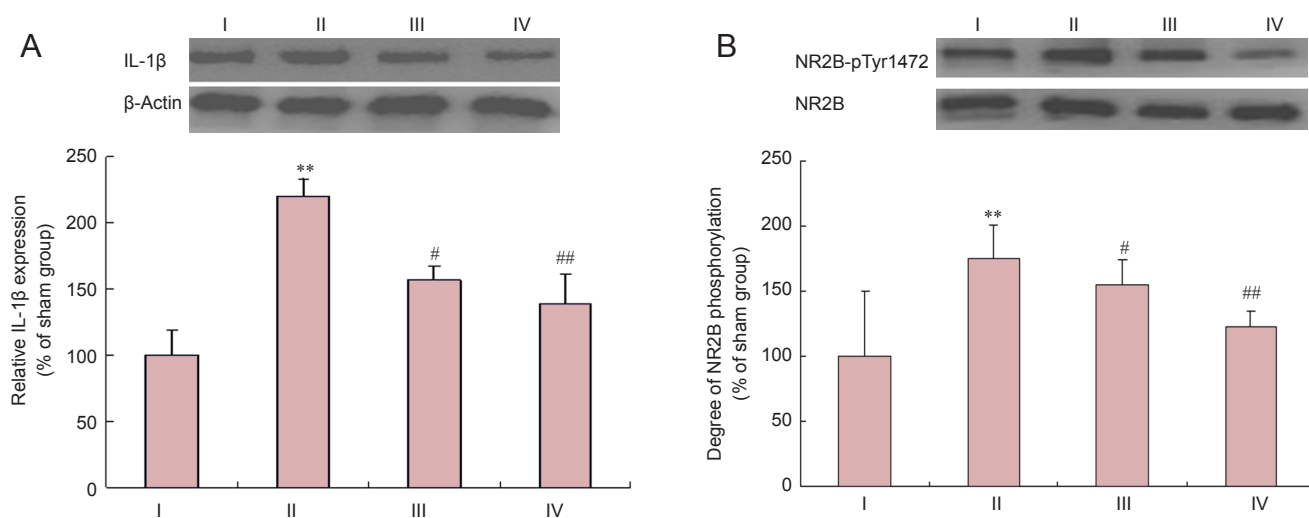


Figure 3 Relative IL-1 β expression (A) and degree of NR2B phosphorylation (B) in the hippocampus (western blot assay).

Data are expressed as the mean \pm SD ($n = 3$ rats per group). The experiment was performed in triplicate. ** $P < 0.01$, vs. sham group; # $P < 0.05$, ## $P < 0.01$, vs. 2VO group (one-way analysis of variance and Bonferroni *post hoc* test). I: Sham; II: 2VO; III: 10 mg/kg Tet; IV: 30 mg/kg Tet. IL-1 β : Interleukin-1 β ; NR2B: N-methyl-D-aspartate receptor 2B; NR2B-pTyr1472: NR2B phosphorylated at tyrosine 1472.

protein per hemi-hippocampus in three rats from each group was extracted with radioimmunoprecipitation assay buffer (Beyotime Institute of Biotechnology, Nanjing, China) and centrifuged at $12,000 \times g$ for 10 minutes. The supernatant was collected, mixed with loading buffer, and boiled for 5 minutes. Polyacrylamide gel electrophoresis was conducted in an 8% separating gel and 5% stacking gel at 60 V for 150 minutes. Proteins were transferred to a 0.45 μm polyvinylidene difluoride membrane. The membrane was blocked with 5% skimmed milk for 2 hours, incubated at 4°C overnight with rabbit anti-rat IL-1 β polyclonal antibody (1:200; Bios Company, Nanjing, China), rabbit anti-rat NR2B polyclonal antibody (1:500; Santa Cruz Biotechnology, Santa Cruz, CA, USA), and rabbit anti-rat NR2B-pTyr1472 monoclonal antibody (1:500; Santa Cruz Biotechnology). After three washes with a mixture of Tris-buffered saline and 0.1% Tween-20, the membrane was incubated with horseradish peroxidase-labeled goat anti-rabbit secondary antibody (ZB-2301, 1:5,000; Zhongshan Golden Bridge Biotechnology Company, Beijing, China) for 1.5 hours at 37°C, and washed three times with Tris-buffered saline and Tween-20. Samples were developed with BeyoECL Plus (P1008, Beyotime Institute of Biotechnology). Bands were then scanned and optical density values were analyzed in a gel imaging system (Chemidoc XRS; Bio-Rad, Hercules, CA, USA). The experiment was performed in triplicate.

Statistical analysis

Data are expressed as the mean \pm SD. Group differences were compared by one-way analysis of variance followed by Bonferroni's multiple comparison test, using IBM SPSS Statistics (version 20.0). $P < 0.05$ was considered statistically significant.

Results

Tet improved cognition in rat models of vascular dementia

In all groups, the mean latency for finding the hidden platform decreased over 5 days (Figure 1A). Latency was

longest in the 2VO group, and significantly shorter in both Tet groups ($P < 0.01$, vs. 2VO). The time spent in the target quadrant by rats in the 2VO group was 40.84% of that in the sham group ($P < 0.01$; Figure 1B). However, administration of Tet at 10 mg/kg or 30 mg/kg resulted in improvements in target quadrant swimming times of 36.95% and 43.3%, respectively ($P < 0.01$, vs. 2VO).

Tet improved hippocampal pathology in rat models of vascular dementia

Hematoxylin-eosin and Nissl staining showed distinct layers in the structure of the hippocampus in the sham-operated rats. Cells had well-defined boundaries with no shrinkage or cytoplasmic disintegration (Figure 2A-a1). In comparison, the hippocampi of rats in the 2VO group showed neurons undergoing colliquative necrosis (Figure 2A-b1), characterized by cytoplasmic dissolution, nuclear shrinkage or disappearance, cell membrane rupture, cell lysis and tissue disorganization. The percentage of living cells in the hippocampal CA1 region of rats in the 2VO group was significantly lower than that in the sham group ($P < 0.01$). However, model rats that received Tet had a higher percentage of living cells than the 2VO group ($P < 0.01$), with no significant difference between the 10 and 30 mg/kg doses. Furthermore, there were fewer Nissl granules in animals that underwent 2VO surgery compared with the sham group (Figure 2A-a2-d2), and administration of 10 or 30 mg/kg Tet resulted in a noticeable recovery in the number of Nissl granules (Figure 2A-c2, 2d2).

Tet increased IL-1 β expression and NR2B phosphorylation in hippocampus of rat models of vascular dementia

Western blot assay showed that IL-1 β expression was significantly higher in the 2VO group than in the sham group ($P < 0.01$) (Figure 3). After administration of Tet at 10 mg/kg ($P < 0.05$) or 30 mg/kg ($P < 0.01$), IL-1 β expression was lower than that in the 2VO group (Figure 3A). Interestingly,

the NR2B-pTyr1472/NR2B ratio followed a similar trend to changes in IL-1 β expression. NR2B phosphorylation was significantly greater in the 2VO group than in the sham group ($P < 0.01$). Administration of Tet at a dose of 10 mg/kg ($P < 0.05$) or 30 mg/kg ($P < 0.01$) resulted in lower NR2B phosphorylation levels than in the 2VO group (**Figure 3B**).

Discussion

We performed bilateral surgical occlusion of the common carotid arteries to establish a rat model of chronic vascular dementia (Wang et al., 2004; Ivy et al., 2010; Valadares et al., 2010). The model resulted in impairments in spatial learning and memory as assessed in the Morris water maze. Longer escape latencies and shorter swim times in the target quadrant were observed in the model rats than in sham-operated rats. This condition was markedly improved after administration of 10 or 30 mg/kg Tet, which resulted in a 49.4% and 55.6% improvement in escape latency, respectively, and a 40.1% and 64.0% increase in target quadrant swimming time. Hematoxylin-eosin and Nissl staining revealed colliquative necrosis in hippocampi of the 2VO group, but less necrosis in the Tet groups than in the 2VO group. The percentages of living cells in the hippocampal CA1 region in the 2VO, 10 mg/kg Tet and 30 mg/kg Tet groups were 46.8%, 86.4% and 91.3%, respectively. These results demonstrated the success of the model, and indicated the potential therapeutic effects of Tet for chronic vascular dementia (Li et al., 2007; He et al., 2011).

High IL-1 β levels are correlated with poor cognitive performance (Munoz et al., 2007; Baune et al., 2008), as reflected in our water maze experiment. Our results were consistent with previous reports of 2VO dementia models showing higher IL-1 expression than sham-operated animals (Zhang et al., 2013; Ben Menachem-Zidon et al., 2014; Rivera-Escalera et al., 2014), suggesting that IL-1 is an important molecular mediator in the development of experimental dementia in the rat. It is interesting to note that the ratio of NR2B-pTyr1472 to NR2B showed a similar trend of change to IL-1 β levels among the experimental groups. Recent studies have shown that IL-1 β regulates various classical neurotransmitter systems (Balosso et al., 2008) and can markedly enhance NMDAR function (Viviani et al., 2003; Salter and Kalia, 2004; Viviani et al., 2006). Overstimulation of the NMDAR represents a key event in Alzheimer's disease, the most common cause of dementia worldwide (Kaul et al., 2001; Haughey and Mattson, 2002). In the present study, hypophosphorylation of NR2B-pTyr1472 may contribute to the induction of typical necrosis, characterized by cytoplasmic dissolution, nuclear shrinkage or disappearance, cell membrane rupture, cell lysis, and Nissl body disappearance. Viviani et al. (2006) showed that recombinant IL-1 β potentiates neuronal death induced by NMDAR activation in primary hippocampal neurons with increased phosphorylation of NR2B at tyrosine 1472. Given this, we propose that IL-1 β may contribute to neuronal necrosis by potentiating NR2B tyrosine phosphorylation. This provides a possible mechanistic explanation for vascular dementia-related inflammation, which is in contrast to previous studies suggesting that

inflammatory disorders can increase the risk of Alzheimer's disease by altering the amyloid- β burden in the brain (Kennedy et al., 2014; Loeffler, 2014; Ostrovskaya et al., 2014).

Tet is an anti-inflammatory Chinese herb that has already been used for the treatment of cancer (Chen et al., 2014; Kang et al., 2014; Wu et al., 2014; Mei et al., 2015; Xiao et al., 2015) and cerebral ischemia/reperfusion injury (Liu et al., 2001; Chen et al., 2011; Ruan et al., 2013). Our results provide evidence of the therapeutic effects of Tet against vascular dementia in a rat model. Further study of the relationship between IL-1 β and the NR2B-pTyr1472/NR2B ratio at the cellular level is warranted (Jing et al., 2010; Wang et al., 2011; Di Filippo et al., 2013; Hwang et al., 2013; Rai et al., 2013). We have investigated only one of several inflammatory pathways involving IL-1 β ; the mechanisms underlying the therapeutic effects of Tet in vascular dementia need further elucidation.

Author contributions: YLL designed this study, collected data and prepared the paper. ZZW was responsible for statistical analysis. LXC designed this study and obtained funding. BXW, LLC, GCQ, BG and JYZ were responsible for literature search. All authors approved the final version of the paper.

Conflicts of interest: None declared.

Plagiarism check: This paper was screened twice using Cross-Check to verify originality before publication.

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