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Research Article

PI3K/Akt/mTOR pathway participates in neuroprotection by dexmedetomidine inhibits neuronic autophagy following traumatic brain injury in rats

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ABSTRACT

Dexmedetomidine (Dex) has been demonstrated to provide neuroprotective effect against brain injury in the central nervous system. However, the underlying mechanism of this neuroprotection remains unclear. In this study, we explored whether Dex has the protective potential in rat models of traumatic brain injury(TBI). More importantly, our study further investigated the role of neuronic autophagy induced by PI3K/Akt/mTOR pathway in this neuroprotective action. Adult male Sprague-Dawley rats were subjected to a diffuse cortical impact injury caused by a modified weight-drop device and Dex (15ug/kg, i.v.) was administered immediately after TBI.

Wet-dry weight method was used to evaluate brain edema. Motor function outcome was assessed by Neurologic Severity Score and the spatial learning ability was evaluated in a Morris water maze. The co-localization of microtubule-associated protein 1 light chain 3(LC3) and neuronal nuclei (NeuN), or LC3 and mammalian target of rapamycin (mTOR) were analyzed by immunofluorescence respectively. The expression of LC3, Phosphorylated protein kinase B (p-Akt) and p-mTOR were quantified using Western blot analysis. Our results showed treatment of rats exposed to TBI with Dex caused not only marked reduction in cerebral edema, motor and cognitive functions deficits, but also a decrease in LC3 levels and a increase in p-Akt and p-mTOR levels. Taken together, these findings indicated that treatment with Dex after TBI could inhibited neuronic autophagy in the hippocampus mediated by the activation of the PI3K/Akt/mTOR pathway, finally promoting neurological recovery.

Keywords: TBI, Dex, Autophagy, Neuroprotection, Hippocampus

Abbreviations: TBI, Traumatic brain injury; Dex, Dexmedetomidine; LC3, Light chain 3; NeuN, Neuronal nuclei; mTOR, Mammalian target of rapamycin; Akt, Protein kinase B

INTRODUCTION

TBI, a leading cause of death and disability all over the world, is one of the major reasons for hospital admissions in modern life.[1] Additionally, the long term medical care and loss of income create a considerable social and economical burden, which remains an unsolved major public health problem globally.[2] Management of TBI can pose enormous challenges to the health team.[3] Mechanical disruption of neurons triggers a cascade of events leading to neuronal cell death, brain edema and neurological impairment following TBI.[4] Yet, cell death is broadly classified into three types: necrosis, apoptosis and autophagy. Interestingly, some studies suggested that autophagy was activated after TBI, and the expression of LC3 and becline-1 were upregulated in the damage hippocampus and cortex.[5] Moreover, other studies indicated inhibition of autophagy involved in the pathogenesis of TBI attenuated traumatic damage and

functional outcome deficits.[6] Currently, Extensive researches, aimed at finding effective strategies and drugs to promote brain damage recovery, have demonstrated that Dex have a significant neuroprotective effects in neurological diseases.

Dex, a potent and highly selective a_2-adrenoceptor agonist, provides hypnotic, sedative, anxiolytic, sympatholytic, and analgesic properties without producing significant respiratory depression.[7,8] Therefore, Dex is widely used in the operating room and intensive care unit for anesthesia and sedation. Sympatholytic effects of Dex are to induce mean arterial blood pressure and heart rate by decreasing norepinephrine release with low concentrations.[9] Recently, A number of studies have demonstrated that Dex treatment may confer neuroprotection against ischemic cerebral injury.[10-12] Dex has also been reported to improve neuron survival in animals subjected to cerebral ischemia/reperfusion injury.[11] In addition, both in vitro and in vivo evidence indicated that Dex could exert a cell-protective effect on nervous tissue under ischemic conditions.[13] These neuroprotective effects of Dex against cerebral injury is associated with increasing the expression of brain-derived neurotrophic factors, stimulating astrocytic a_2-adrenergic receptors and increasing astrocytic calcium concentrations. Furthermore, There is recent evidence suggesting that Dex may inhibit the release of neurotoxic glutamate, stimulate glutaminase activity and promote astrocytes to eliminate glutamine, thereby reducing excitotoxicity and ameliorating toxic effects.[14] Interestingly, Dex was reported to increase the levels of anti-apoptotic factor BCL-2 and extracellular-signal-regulated kinase (ERK) 1/2 phosphorylation involved in cell survival, which would inhibit neuroapoptosis and improve neuronal survival in brain injury.[15,16] Currently, The PI3K/Akt/mTOR has been widely reported to be the classical signaling pathway of apoptosis and autophagy activation.[17]

Based on the above-mentioned findings, We hypothesized that administration Dex may activate the PI3K/Akt/mTOR pathway to suppress neuronic autophagy in the hippocampus, exerting a powerful neuroprotective effects against TBI in rats.

METHODS

Animals. All experiments procedures were carried out in accordance with the guidelines of the Chinese Council on Animal Protection and were approved by Hebei United University Committee for the use of animals in research. A total of 120 male Sprague-Dawley (SD) rats, aged 12-16 weeks and weighing 350-375 g (Vital River Laboratory Animal Technology Co. Ltd. Beijing, China) were used in the present study. All animals were housed with a standard of 12 h light/dark cycle and free access to water and food before and after surgery or sham operation.

Preparation of TBI model. The rat model of TBI was induced by using a modified weight-drop device, as described previously by Marmarou.[18] Briefly, the rats were anaesthetised with sodium pentobarbial (Nembutal 60 mg/kg). After a midline incision was made to expose the skull between bregma and lambda suture lines, a steel disc (10 mm in diameter and 3 mm in thickness) was adhered to the skull using dental acrylic. Animals were moved onto a foam mattress underneath a weight-drop device where a weight of 450g falls freely through a vertical tube from 1.5 m onto the steel disc. Sham-operated animals underwent the same surgical procedure without weight-drop impact. Rats were housed in individual cages after surgery and placed on heat pads (37°C) for 24 h to maintain normal body temperature during the recovery period.

Group and drugs administration. The total of 120 male SD rats were randomly divided into three groups: sham-operated group, TBI group, and TBI treated with Dex group. Every sub-group was composed of 10 rats and the rats were killed at the point of 6 h, 12 h, 24 h and 48 h after TBI. Animals with TBI received Dex (15ug/kg, Hengrui Pharmaceutical Co. Jiangsu, China) with i.v. injection 1 h after TBI.

Evaluation of brain edema. Brain edema was evaluated by analysis of brain water content with the wet-dry weight method as described previously.[17] Animals were sacrificed by decapitation under deep anesthesia at 24 h and 48 h following TBI or sham operation. Brains were separated and weighed immediately to get wet weight. Following drying in a desiccating oven for 24 h at 100°C, dry tissues were weighed again. The percentage of water in the tissues was calculated according to the formula: % brain water=[(wet weight−dry weight) /wet weight] ×100.

Recovery of motor function. The neurobehavioral status of the rats was evaluated using a set of 10 tasks, collectively termed Neurologic Severity Score (NSS), which tests reflexes, alertness, coordination, and motor abilities. One point is awarded for failure to perform a particular task, thus, a score of 10 reflects maximal impairment, whereas a normal rat scores 0.[19] Post-injury, NSS was evaluated at 24 h and 48 h. Each animal was assessed by an observer who was blinded to the animal treatment. The difference between the initial NSS and that at any later time was calculated for each rat, and this value (∆NSS) reflects the spontaneous or treatment-induced recovery of motor function.

Morris water maze test. The spatial learning ability was assessed in a Morris water maze as described previously.[20] The Morris water maze consists on a black circular pool (180 cm diameter, 45 cm high) filled with water (30 cm depth) at 26 °C and virtually divided into four equivalent quadrants: north (N), west (W), south (S) and east (E). A 2-cm submerged escape platform (diameter 12 cm, height 28 cm, made opaque with paint) was placed in the middle of one of the quadrants equidistant from the sidewall and the center of the pool. Rats were trained to find the platform before TBI or sham

operation. For each trial, the rat was randomly placed into a quadrant start points (N, S, E or W) facing the wall of the pool and allowed a maximum of 60 sec to escape to a platform, if failed to escape within 90 sec and was allowed to stay in the platform for 20 sec maximum before returning home cage for a new trial (intertrial interval 20 sec). Maze performance was recorded by a video camera suspended above the maze and interfaced with a video tracking system (HVS Imaging, Hampton, UK). The escape latency of a total of five trials were averaged in the water maze testing. This test was conducted at 24 h and 48 h after TBI.

Western blot analysis. Western blotting was conducted as described previously.[21] Briefly, the rats were deeply anesthetized and underwent an intracardiac perfusion with 0.1 mol/L phosphate-buffered saline (PBS; pH 7.4). The hippocampal CA1 were rapidly isolated; total proteins were extracted, and protein concentration was determined by the BCA reagent (Solarbio, Beijing, China) method. Samples were subjected to sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE). Separated proteins on the gel were transferred onto PVDF membranes (Roche Diagnostics, Mannheim, Germany). Blots were blocked with 5% fat-free dry milk for 1 h at room temperature. Subsequently, Blots were incubated overnight at 4°C with indicated primary antibodies, including rabbit anti-LC3 polyclonal antibodies, rabbit anti-p-AKt polyclonal antibodies, rabbit anti-p-mTOR polyclonal antibodies or rabbit anti-β-actin polyclonal antibodies (Santa Cruz Biotechnology, Santa Cruz, CA, USA, diluted 1:500), Then the blots were incubated with horseradish peroxidase conjugated anti-rabbit IgG (Cell Signaling Technology, Inc., Danvers, MA, USA, diluted 1:5000) for 2 h at room temperature. After incubation with a properly titrated second antibody, the immunoblot on the membrane was visible after developing with an enhanced chemiluminescence (ECL) detection system and the densitometric signals were quantified using an imaging program. Immunoreactive bands of all proteins expression were normalized to the intensity of corresponding bands for β-actin. The Western blot results were analyzed with National Institutes of Health Image 1.41 software (Bethesda, MD, USA).

Immunofluorescence analyses. The brain tissues were fixed in 4% paraformaldehyde for 24 h, taken into 30% sucrose solution (0.1 M PBS, pH 7.4) until sinking to the bottom, 200 um apart from each section from anterior to posterior hippocampus (bregma -1.90 to-3.00) were made from TBI animal and then embedded in OCT. 15 μm frozen sections were sliced with frozen slicer, treated with 0.4% Triton-100 for 10 min, and blocked in normal donkey serum for 1 h. For double labeling, the frozen sections were incubated with a mixture of rabbit anti-LC3 polyclonal antibody (diluted 1:100) and mouse anti-NeuN (or mTOR) polyclonal antibody (Santa Cruz Biotechnology; Santa Cruz, CA, USA diluted 1:100) overnight at 4℃. The next day, the sections were incubated with a mixture of fluorescein-conjugated anti-rabbit IgG and anti-mouse IgG (Santa Cruz Biotechnology; Santa Cruz, CA, USA, diluted 1:1000) for 2 h at 37°C in the dark. Photographs were taken in a laser scanning confocal microscope (OLYMPUS FV1000). Primary antibodies were replaced with PBS in the negative control group.

Statistical analysis. Data were expressed as mean ± standard error. SPSS 16.0 (SPSS, Chicago, IL) was used for statistical analysis of the date. Statistical analysis was performed using ANOVA and followed by the Student-Newman-Keuls post-hoc tests or Student t-test (two means comparison). *P* value of less than 0.05 was considered statistically significant.

RESULTS

Dex Treatment attenuates TBI-induced cerebral edema. The wet-dry weight method was used to evaluate brain edema. As shown in Figure 1, the degree of brain edema was significantly increased compared with the sham-operated group at 24 h and 48 h after trauma. Treatment with Dex markedly diminished the increment of brain edema compared with the TBI group at the corresponding time, all of which were still higher than in the sham-operated group.

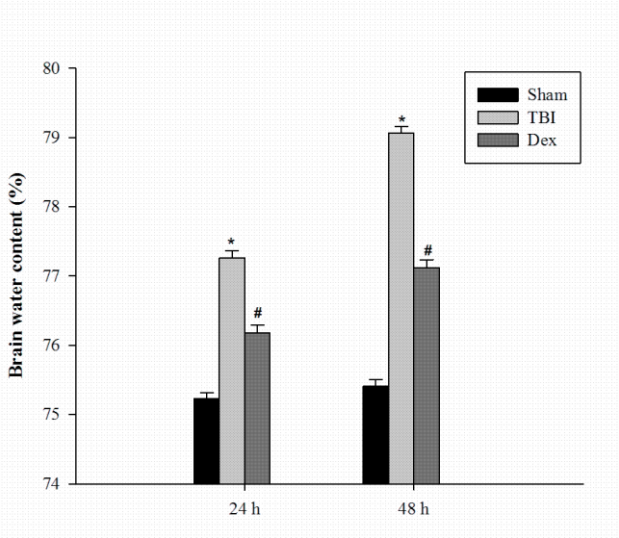

Figure 1: The effect of Dex on TBI-induced brain edema. Brain water content was determined at 24 h and 48 h following TBI. Bars represent mean ± standard error (n=5). Brain water content increased markedly at 24 h and 48 h post TBI. Administration of Dex significantly decreased brain edema at 24 h and 48 h as reflected by a decrease in brain water content. *$P<0.05$, vs. sham group, $^{\#}P<0.05$, vs. TBI group at the same time point.

Dex Treatment attenuated TBI-induced motor deficits. The temporal changes in functional recovery of the rat, expressed as ΔNSS. As shown in Figure 2, TBI elicited a

significant decline in motor performance as reflected by a increase in ΔNSS at 24 h and 48 h after TBI. In marked contrast, post-injury administration of Dex significantly decreased ΔNSS score, suggesting Dex treatment could improve the recovery of motor functional outcome after TBI.

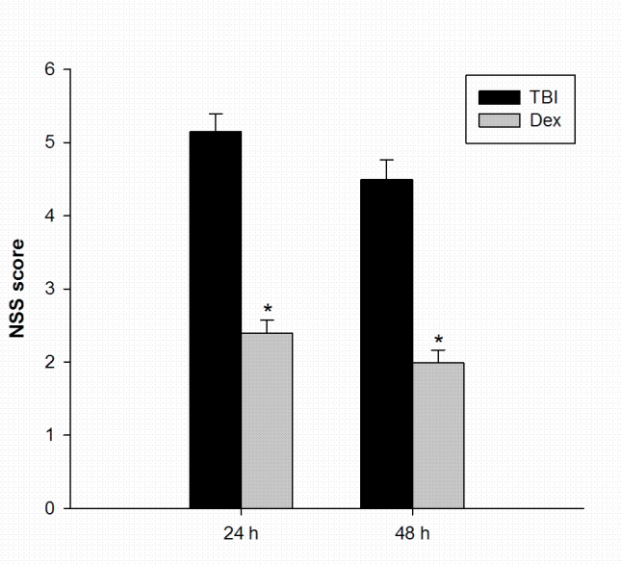

Figure 2: The effect of Dex on TBI-induced motor deficits. The temporal changes in motor recovery of the rat was determined at 24 h and 48 h after TBI. Bars represent mean ± standard error (n=5). After TBI, motor impairment was observed as revealed by a increase in ΔNSS. Dex significantly improved motor function at 24 h and 48 h post TBI as reflected by a decrease in ΔNSS. *$P<0.05$, vs. TBI group at the same time point.

Dex Treatment attenuated TBI-induced learning deficits. The spatial learning function was assessed by Morris water maze at 24 h and 48 h after TBI. As shown in Figure 3, All rats in the TBI group displayed increased latencies in the ability to find the hidden platform compared with the sham group at 24 h and 48 h. The rats subjected to Dex demonstrated a significant decrease in the latencies, relative to animals in the TBI group at 48 h, thereby indicating Dex treatment could result in cognitive functional recovery post TBI.

Dex Treatment inhibites TBI-induced neuronic autophagy. Double immunofluorescence staining was performed to investigate co-localization of LC3 and NeuN expression at 24 h post TBI. As shown in Fig. 4A, LC3 was stained with rabbit anti-LC3 antibody and secondary antibody labeled green fluorescent. At the same time, neurous was stained with mouse anti-NeuN antibody and secondary antibody labeled red fluorescent. After merging, yellow was observed under a laser scanning confocal microscope, indicating the majority of LC3 was mainly located in living neurons. LC3 II protein expression was analyzed by western blot analysis (Fig. 4B or 4C). LC3 II protein was identified at low levels in the hippocampus in the sham group. The of LC3 II in the hippocampus was significantly increaseed at 6 h post TBI, reached a maximum level at 24 h. However, treatment with Dex significantly inhibited the upregulation of LC3 II levels compared with the TBI groups at 6 h, 12 h and 24 h. These results clearly showed that Dex treatment drastically suppressed activation of neuronic autophagy following TBI.

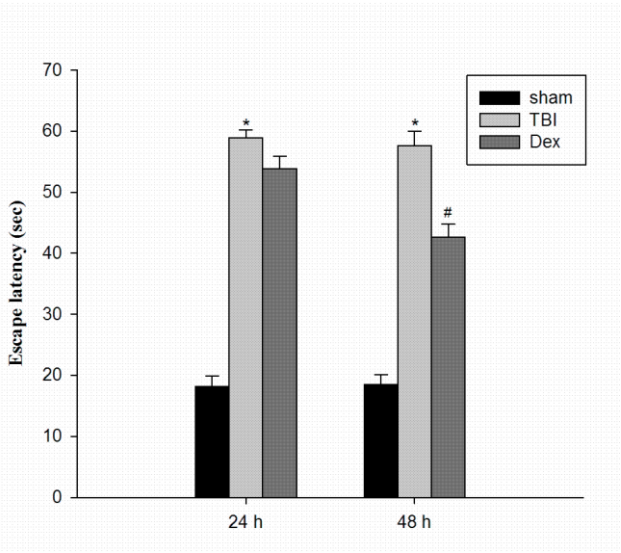

Figure 3: The effect of Dex on TBI-induced learning deficits. The escape latency performance was evaluated by Morris water maze at 24 h and 48 h after TBI. Bars represent mean ± standard error (n=5). The escape latency significantly increased at 24 h and 48 h post TBI. Animals subjected to treatment with Dex demonstrated a significant decrease the time to identify the platform at 48 h. *$P<0.05$, vs. sham group, $^{\#}$ $P<0.05$, vs. TBI group at the same time point.

Dex Treatment activates PI3K/Akt/mTOR pathway. Double labeling with LC3 and mTOR proteins to show the relationship between autophagy and mTOR pathway after TBI. As shown in Fig. 5A, LC3 was stained with rabbit anti-LC3 antibody and secondary antibody labeled green fluorescent. At the same time, mTOR was stained with mouse anti- mTOR antibody and secondary antibody labeled red fluorescent. After merging, yellow was observed under a laser scanning confocal microscope, Our results indicated mTOR signaling pathway was involved in the process of autophagy activation. The expression Akt and mTOR in the hippocampus was not significantly different among all groups (data not shown). the levels of p-Akt (Fig. 5B or 5D) and p- mTOR (Fig. 5C or 5E) were determined by western blot analysis. The expression of p-Akt and p-mTOR protein in the hippocampus were significantly downregulated at 6 h, 12 h, 24 h and 48 h after TBI.

Treatment with Dex markedly reversed the decrease in p-Akt and p-mTOR levels in the hippocampus at all correspondence time points. These dates demonstrated that activation of PI3K/Akt/mTOR pathway might be involved in mediating the effect of Dex against neuronic autophagy after TBI in rats.

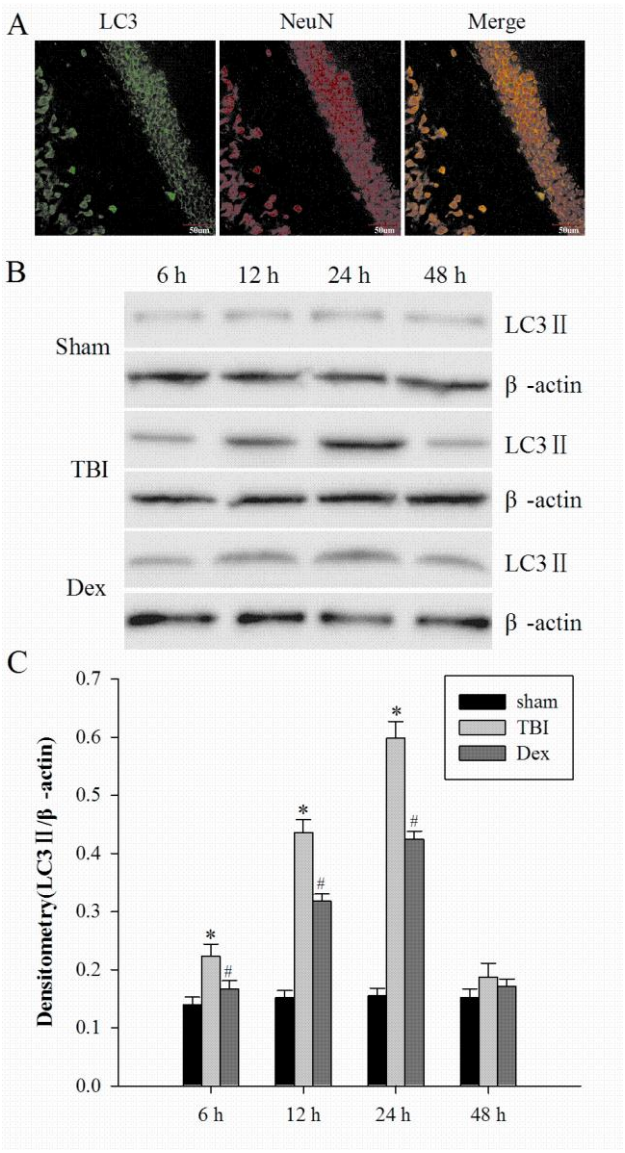

Figure 4: The effect of Dex on TBI-induced neuronic autophagy. Confocal images of LC3 and NeuN(A). LC3 immunoreactivity (green) was present in NeuN-positive cells (red) 24 h after TBI. Overlay of LC3 (green) and NeuN (red) showed specificity of LC3 for neuron cells. All microphotographs were visualized by confocal laser scanning microscopy. Scale bar: 50um. Treatment with Dex prevented TBI-induced LC3 II activation. Protein levels of LC3 II in the hippocampus (B) were detected with immunoblotting and densitometry analysis of LC3 II band corresponding to β-actin (C). Bars represent mean ± standard error (n=5). *$P<0.05$, vs. sham group, $^{\#}P<0.05$, vs. TBI group at the same time point.

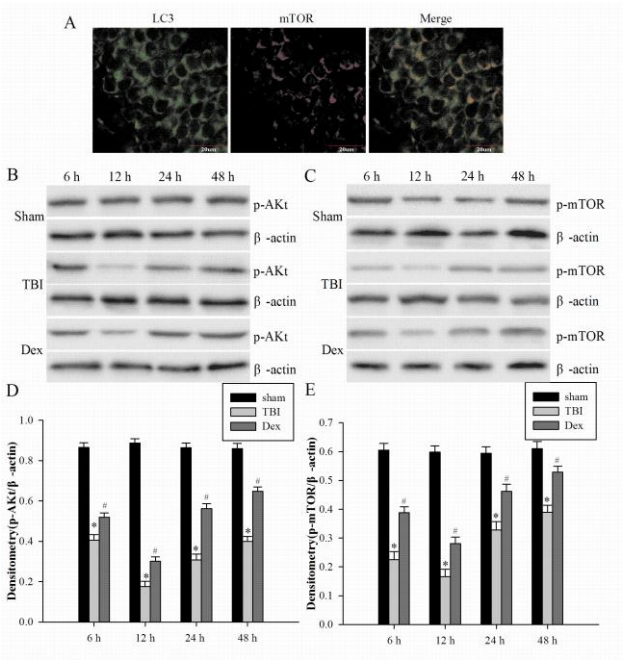

Figure 5: The effect of Dex on PI3K/Akt/mTOR pathway involved in neuronic autophagy. Confocal images of LC3 and mTOR (A). Overlay of LC3 (green) and mTOR (red) showed yellow fluorescent. All microphotographs were visualized by confocal laser scanning microscopy. Scale bar: 20um. treatment with Dex reversed TBI-induced the decrease in p-Akt and p-mTOR protein. The expression of p-Akt (B)and p-mTOR(C) in the hippocampus were detected with immunoblotting and densitometry analysis of p-Akt (D) or p-mTOR(E) band corresponding to β-actin. Bars represent mean ± standard error (n=5). *$P<0.05$, vs. sham group, $^{\#}P<0.05$, vs. TBI group at the same time point.

DISCUSSION

In this study, we found that systemically administered Dex could especially decrease the degree of brain edema post TBI, which exerted a protective effect in rats exposed brain injury. It has been reported that Dex improved neurologic outcome in cerebral I/R injury,[11] so we sought to perform motor and memory function experiments in rat models of TBI. The hippocampus is one of the more widely studied structures related with spatial memory. the Morris water maze has been widely used in rodents to study for spatial learning ability many years.[22] All results of Neurologic Severity Score and Morris water maze showed that a single injection of Dex immediately following TBI significantly improved motor and learning function deficits. These findings suggested that Dex confered neuroprotection against TBI in rats. However, the specific molecular mechanisms is not yet completely understood. Noticeably, our studies revealed that Dex could suppresse neuronic autophaghy and improve neuronal survival in the hippocampus after TBI in rats.

Autophaghy, an evolutionarily conserved pathway, is the chief machinery for bulk degradation of proteins and entire organelles in cells undergoing stress.[6] LC3, a mammalian homologue of yeast ATG8, is one of the most reliable biomarkers in the study of autophagy induction. We detected biochemical evidence of autophagosomal vacuole formation, a shift from LC3 I to II after TBI in rats. Furthermore, using immunostaining and confocal microscopy to investigate the distribution of LC3. Our results suggested the increased LC3 immunostaining was found mainly in neurons of the damage hippocampus under confocal microscopy, consistent with our previous studies.[5,23] Immunoblotting demonstrated a significant elevation in LC3II levels from 6 h to 24 h post-TBI. These results clearly showed that autophagy was activated significantly after TBI. In particular, we have previously shown that autophagy is highly induced in CA1 neurons of rats hippocampus after TBI.[24] More interestingly, treatment with Dex after TBI partially inhibited traumatic-elicited induction of LC3II immunoreactivity, indicating autophagy is involved in the Dex-induced protection against the cerebral injury. Consequently, We speculated that nueroprotective effects by Dex against cerebral injury was accompanied by the inhibition of autophagy acivation in the hippocampus.

Even though the exact mechanism of against neuronic autophagy remains unclear, activation of the PI3K/Akt/mTOR pathway is able to be one of the key factors. Activation of PI3K/Akt/mTOR has been widely reported to participate in the protection by pharmacological treatment against cerebral injury.[25] The fact that PI3K/Akt/mTOR signaling pathway plays a pivotal role in cell growth, proliferation and survival has been widely reported.[26] Fourthermore, the mTOR pathway has been linked to autophagy and cell death.[17] Autophagy activation after TBI is largely dependent on mTOR pathway in rats.[27] immunoblotting results revealed the expression of p-Akt and p-mTOR proteins was decreased in the damage hippocampus CA1 after TBI in rats, suggesting the decrease in p-Akt and p-mTOR induced autophagy activation. However, the down-regulation of p-Akt and p-mTOR in the hippocampus post-TBI was reversed by Dex treatment. These results showed that Dex potently protected neurons of the hippocampus against autophagic death and this protection may be mediated by PI3K/Akt/mTOR signaling pathway.

In conclusion, our study demonstrated that treatment with Dex not only reduced cerebral edema, but also improved motor and cognitive outcome deficits in rats exposed to TBI. The autophagic mechanisms participated in the protective effect by Dex against brain damage and neurologic outcome deficits after TBI. Strikingly, we confirmed administration of Dex could inhibit neuronic autophagy in the hippocampus, which may be mediated by activation of the PI3K/Akt/mTOR signaling pathway.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Animal Ethics Committee

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