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Research article

Prolonged hydrocephalus induced by intraventricular hemorrhage in rats is reduced by curcumin therapy

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HIGHLIGHTS

- The autologous blood intraventricular injection would lead to acute intraventricular hemorrhage (IVH) and prolonged hydrocephalusin.
- Curcumin treatment alleviates chronic BBB damage post-IVH induction through protecting the impaired neurovascular units.
- The incidence of post-hemorrhagic hydrocephalus is reduced by curcumin.

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ABSTRACT

Prolonged hydrocephalus is a major cause of severe disability and death of intraventricular hemorrhage (IVH) patients. However, the therapeutic options to minimize the detrimental effects of post-hemorrhagic hydrocephalus are limited. Curcumin has been reported to confer neuroprotective effects in numerous neurological diseases and injuries, but its role in IVH-induced hydrocephalus has not been determined. The aim of present study was to determine whether curcumin treatment ameliorates blood brain barrier (BBB) damage and reduces the incidence of post-hemorrhagic hydrocephalus in IVH rat model. Autologous blood intraventricular injection was used to establish the IVH model. Our results revealed that repeated intraperitoneal injection of curcumin ameliorated IVH-induced learning and memory deficits as determined by Morris water maze and reduced the incidence of post-hemorrhagic hydrocephalus in a dose-dependent manner at 28 d post-IVH induction. Further, the increased BBB permeability and brain edema induced by IVH were significantly reduced by curcumin administration. In summary, these findings highlighted the important role of curcumin in improving neurological function deficits and protecting against BBB disruption via promoting the neurovascular unit restoration, and thus it reduced the severity of post-hemorrhagic hydrocephalus in the long term. It is believed that curcumin might prove to be an effective therapeutic component in prevent the post-IVH hydrocephalus in the near future.

1. Introduction

Intraventricular hemorrhage (IVH) occurs secondary to nearly half of patients with spontaneous intracerebral hemorrhage (ICH), which acts as an independent predictor of unfavorable outcomes [15]. Due to lack of understanding of how cerebral ventricular dilation happens following IVH, there are still no targeted preventive therapy for prolonged hydrocephalus [14]. It is thus obvious that the clearance of hematoma from the ventricles should be a therapeutic goal for IVH patients with acute intracranial hypertension. But in cases of chronic hydrocephalus following IVH, external ventricular drainage has been proven often insufficient [16]. Intraventricular fibrinolysis (IVF) seems to be beneficial at least in the context of spontaneous ICH, in which their use is now accepted but not yet validated by randomized controlled trial [18,11] The endoscopic retrieval of intraventricular hematoma was also considered an efficient method to improve the outcomes of IVH patients in recent study, but it can only be carried out in limited neurosurgical centers [10]. To explore a valid therapy for IVH represents a critical challenge for neurosurgeons, neurologists, and intensivists.

Curcumin, a low-molecular-weight phenolic pigment derived from the Curcuma longa, was reported with anti-inflammatory,

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anti-fibrosis and anti-oxidant effects. Previous studies demonstrated that curcumin nanoparticles permeated the blood brain barrier (BBB), induced adult neurogenesis through activating the Wnt/β-catenin pathway, and thus improved the cognitive disorder of Alzheimer's disease. Several studies have shown that curcumin reduced ICH-induced BBB damage and brain edema though inhabiting matrix metalloproteinases expression [22,25]. Besides, Liu W et al. has recently reported administering curcumin alleviated neuro-inflammation post-ICH induction which plays a critical role in the BBB damage, at least in part by reducing the infiltration of T lymphocytes into brain [24]. Moreover, the long-term neuroprotective effect of curcumin was also confirmed in the chronic stage of spinal cord injury though inhabiting the expression of proinflammatory cytokines [6].

Therefore, we used a rat model of IVH to test the hypothesis that curcumin treatment alleviate the blood brain barrier rupture following IVH, thereby reducing the severity of chronic hydrocephalus and improving neurological functions in the present study.

2. Material and methods

2.1. Animals

One hundred and fifty-seven adult male Sprague-Dawley rats weighing 280–380 g were provided by the Experimental Animal Center of Third Military Medical University in present study. All experimental protocols were approved by the Ethic Committee of Third Military Medical University, and performed in accordance with the Guide for the Care and Use of Laboratory Animals. Rats were housed in a temperature- and humidity-controlled and 12-h light/dark cycle environment and with food and water ad libitum. The experimental animals were randomly assigned into following groups, including Sham (sham-operated, n = 37), IVH (vehicle-treated IVH, n = 40), IVH + Cur 100 mg/kg (Curcumin 100 mg/kg daily intraperitoneal injection after IVH, n = 40), and IVH + Cur 300 mg/kg (Curcumin 300 mg/kg daily intraperitoneal injection after IVH, n = 40).With operation completed, first dose was administered immediately and all drugs were administered for the first 7 d. Curcumin was purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, US).

2.2. IVH model

The establishment of the IVH model was induced by autologous blood stereotaxic injection into ventricle as previously described [14]. Briefly, after anesthetization, the head was mounted on a stereotaxic frame, and a 30-gauge needle was inserted into the right lateral ventricles (coordinates: 1 mm posterior, 3.5 mm ventral, and 1.5 mm lateral to the Bregma); 200 ul autologous blood, taken from the right femoral artery, were infused into lateral ventricle within 10 min using a micro-infusion pump. Only a needle injection in the same location was given to the rats in Sham group. All surgical procedures were conducted under aseptic conditions and the animals were kept at approximately 37.0 ± 0.5 °C on an electric heating blanket.

2.3. Morris water maze test

Spatial learning and memory performance was assessed by Morris water maze (MWM) test between day 21–26 following surgery, which consisted of 5-day training (visible platform training sessions) and invisible platform trial session on day 6 (n = 8 for each group). A round pool (120 cm in diameter) was filled with water (24 ± 2 °C) at a depth of 30 cm. A transparent platform (10 cm in diameter) was hidden below the water surface. During the 5-day training, rats was placed in the water and allowed to search for the platform for 120 s until it reached the platform and were allowed to rest for 15 s. If the rat did not reach the platform within 120 s, it was placed on the platform for 15 s. The escape latency time was recorded at each trial. After 5-day training, the platform was removed. The times that rats entered platform area were recorded during 120-s searching at the final trial on day 6.

2.4. MRI and volume measurement

Serial and T2-weighed Imaging was carried out in a 7.0-T Varian MR scanner (Bruker, Germany) at 1 and 28 days post-IVH induction as described before [23](n = 21 for Sham group and n = 24 for the rest groups). Briefly, rats were anesthetized with 2% isoflurane/air mixture throughout the MRI examination. The imaging protocol for all rats included a T2 fast spin-echo sequence using a resolution matrix = 256 × 256, field of view (FOV) = 30 mm × 30 mm and 17 coronal slices (1.0 mm thickness). Bilateral Lateral ventricular volumes were calculated using Image J from the T2 images as described before [11]. Ventricular volume was obtained by combining the cross sectional area measured on all of the brain slices and multiplying them by section thickness (1.0 mm). Volume measurements were performed by a blinded observer.

2.5. Evans blue extravasation

The BBB damage induced by IVH was evaluated via the extravasation of Evans blue (EB) dye at 24 h and 28 d (n = 8 for each group). The EB dye (2%, 5 ml/kg; Sigma–Aldrich Co., St. Louis, MO, USA) was injected into the right femoral vein under anesthesia at 2 h prior to execution. Then rats were euthanized by an intracardial perfusion with sterile saline. After the choroid plexus were removed, the brain samples were divided into the ipsilateral and contralateral hemispheres for the tissue homogenate and weighed. Then equal volume of trichloroacetic acid was added to the resultant supernatant. Those samples from ipsilateral hemispheres were then incubated overnight at 60 °C and centrifuged at 15000*g* for 30 min. The supernatant was then spectrophotometrically collected and quantified for the EB content at O.D. 620 nm (Thermo Scientific, US).

2.6. Brain water content

The severity of brain edema was evaluated by brain water content measure at 24 h and 28 d (n = 8 for each group). After anesthetization, the ipsilateral hemispheres were quickly dissected. All specimens were immediately weighed to obtain the wet weight, and then dried in an oven at 100 °C for 72 h to obtain the dry weight. Brain water content was calculated as (wet weight − dry weight)/wet weight × 100%.

2.7. Statistical analysis

Data are presented as the mean ± standard error of the mean (SEM). Data of Fig. 1-3 were analyzed by one-way ANOVA with post hoc LSD test for multiple comparisons. Data of Table 1 was analyzed by chi-square test. *P* values < 0.05 were considered significant.

3. Results

3.1. Autologous blood injection into ventricle fabricated IVH animal model

Autologous blood ventricle injection was applied to mimic intraventricular hemorrhage in present study. Nearly 80% experimental IVH animals developed chronic hydrocephalus (Table 1). The mortality of blood injected model was 3.1% (n = 5), which mostly

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