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Research report

Glibenclamide pretreatment protects against chronic memory dysfunction and glial activation in rat cranial blast traumatic brain injury

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ABSTRACT

Blast traumatic brain injury (bTBI) affects both military and civilian populations, and often results in chronic deficits in cognition and memory. Chronic glial activation after bTBI has been linked with cognitive decline. Pharmacological inhibition of sulfonylurea receptor 1 (SUR1) with glibenclamide was shown previously to reduce glial activation and improve cognition in contusive models of CNS trauma, but has not been examined in bTBI. We postulated that glibenclamide would reduce chronic glial activation and improve long-term memory function after bTBI. Using a rat direct cranial model of bTBI (dc-bTBI), we evaluated the efficacy of two glibenclamide treatment paradigms: glibenclamide prophylaxis (pre-treatment), and treatment with glibenclamide starting after dc-bTBI (post-treatment). Our results show that dc-bTBI caused hippocampal astrocyte and microglial/macrophage activation that was associated with hippocampal memory dysfunction (rapid place learning paradigm) at 28 days, and that glibenclamide pre-treatment, but not post-treatment, effectively protected against glial activation and memory dysfunction. We also report that a brief transient time-window of blood-brain barrier (BBB) disruption occurs after dc-bTBI, and we speculate that glibenclamide, which is mostly protein bound and does not normally traverse the intact BBB, can undergo CNS delivery only during this brief transient opening of the BBB. Together, our findings indicate that prophylactic glibenclamide treatment may help to protect against chronic cognitive sequelae of bTBI in warfighters and other at-risk populations.

1. Introduction

Primary blast traumatic brain injury (bTBI) results when shock waves generated by an explosive device, chemical or fireworks explosion, or industrial accident delivers energy to brain tissues. In recent years, the incidence of bTBI in the US has risen dramatically, due partially to injuries sustained by US military personnel deployed to Iraq and Afghanistan [1]. In one estimate, approximately 320,000 US military personnel suffered from bTBI between 2001 and 2008 [2].

Many patients with bTBI develop chronic cognitive sequelae, which commonly include chronic memory loss [3,4]. The current therapeutic mainstay for patients with bTBI-induced cognitive deficits is cognitive rehabilitation therapy [5]. However, even with cognitive rehabilitation, patient outcomes are variable, with 10–15% of patients still exhibiting symptoms 12 months after bTBI [6,7]. Therefore, novel therapeutic strategies to improve long-term cognitive function after bTBI are greatly needed.

Neuroinflammation and glial activation occur within minutes after TBI [8,9], and can persist for years-to-decades after injury [9]. Chronic glial activation in the hippocampus is closely associated with hippocampal dysfunction and memory deficits after central nervous system (CNS) injury [10–12,13], and therefore represents an attractive therapeutic target.

Sulfonylurea receptor 1 (SUR1), an ABC transporter that regulates the activity of plasmalemmal ion channels, is upregulated by all CNS cells after TBI [14–16], including bTBI [17]. SUR1 contributes to cellular and vascular dysfunction [18–22], and worsens glial activation after CNS injury [18,23]. Glibenclamide, a SUR1 antagonist [24] that is

Abbreviations: bTBI, blast traumatic brain injury; CNS, central nervous system; SUR1, sulfonylurea receptor 1; dc-bTBI, direct cranial bTBI; BBB, blood-brain barrier; COBIA, cranium only blast injury apparatus; BDCCI, blast dissipation chamber cranium interphase; DMSO, dimethyl sulfoxide; NS, normal saline; FITC, fluorescein isothiocyanate; ANOVA, analysis of variance; K_{ATP}, SUR1-KIR6.2

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well-tolerated by patients [25], has been shown to improve memory function, reduce neuroinflammation, reduce brain edema, reduce contusion volume, minimize secondary hemorrhage, and reduce epileptic seizures after CNS injury [14,15,23,26]. Thus, we postulated that glibenclamide treatment might protect against chronic neuroinflammation and long-term cognitive dysfunction after bTBI.

Whereas glial activation occurs within minutes after TBI [8,9], medical interventions for bTBI often are initiated hours to days after injury. By this time, glial activation is prominent [27], and may be refractory to pharmacological intervention. We reasoned that prophylactic treatment, wherein the time-to-treatment is essentially zero, might more effectively prevent the formation of reactive gliosis and its associated complications, such as memory deficits.

Here, we evaluated the efficacy of glibenclamide prophylaxis (pre-treatment) versus glibenclamide reactive treatment (post-treatment) in preventing cognitive dysfunction after experimental bTBI. We utilized a rat model of direct cranial bTBI (dc-bTBI) that replicates key features of chronic memory loss after human bTBI [28,29]. We report that glibenclamide pre-treatment, but not post-treatment, protects against post-dc-bTBI hippocampal memory deficits and neuroinflammation. We show that transient blood-brain barrier (BBB) dysfunction after dc-bTBI may account for differences in efficacy between glibenclamide pre-treatment and post-treatment. Overall, our findings indicate that prophylactic administration of glibenclamide may help to ameliorate chronic cognitive deficits due to bTBI in warfighters and other at-risk populations.

2. Materials and methods

2.1. Rat direct cranial blast TBI (dc-bTBI)

All surgical procedures were approved by the Institutional Animal Care and Use Committee of the University of Maryland, School of Medicine. This research was conducted in compliance with the Animal Welfare Act Regulations and other federal statutes relating to animals and experiments involving animals, adheres to the principles set forth in the Guide for the Care and Use of Laboratory Animals, National Research Council, 1996, and conforms to the ARRIVE guidelines [30].

Male Long-Evans rats (285–315 gm; Harlan, Indianapolis, IN) were anesthetized (60 mg/kg ketamine and 7.5 mg/kg xylazine, intraperitoneal), intubated with an endotracheal tube, and allowed to breathe room air spontaneously. Core temperature was maintained at 37 °C using an isothermal pad (Deltaphase; Braintree Scientific, Braintree, MA). dc-bTBI was obtained using the Cranium Only Blast Injury Apparatus (COBIA), as previously described [28]. The hair was clipped and the head was positioned in the Blast Dissipation Chamber Cranium Interphase (BDCCI) of the COBIA such that the blast epicenter was 4–8 mm rostral to the occipital crest. A blast wave was generated by detonating a 0.22 caliber smokeless powder cartridge, with a peak overpressure, measured at the BDCCI, of ~ 427 kPa (blast dissipation chamber, 29.5 cm; see reference [28]). Because the device delivers a collimated (25.4 mm) blast wave selectively to the occipital region, there is no “exhaust” or “blast wind” injury due to inhalation of hot gases, and there is no transthoracic, transvascular mechanism of injury [17]. All rats subjected to dc-bTBI experienced apnea immediately after blast, the duration of which was recorded as a measure of the severity of injury. With the peak overpressure chosen, all rats regained spontaneous breathing, mechanical ventilation was not required, and no deaths occurred. Rats were nursed on a heating pad until they recovered spontaneous movements. For pain relief, buprenex 0.15 mL was administered subcutaneously every 8–12 h up to 48 h.

Rats were randomly assigned to one of four treatment groups: vehicle pre-treatment (n = 12), glibenclamide pre-treatment (n = 12), vehicle post-treatment (n = 15), and glibenclamide post-treatment (n = 15). All of these rats were subjected to dc-bTBI, as described above, and later underwent neurofunctional testing. As controls for neurofunctional testing, a fifth group of 12 rats underwent sham injury, with the entire procedure performed as described above, except that the cartridge was not detonated. A sixth group of 41 rats subjected to dc-bTBI or sham injury was used to quantify BBB permeability at different times after dc-bTBI.

2.2. Glibenclamide treatment

Glibenclamide or vehicle stock solutions were prepared, as fully detailed previously [31], by dissolving 25 mg glibenclamide (#G2539; meets USP testing; Sigma, St. Louis, MO) in 10 mL dimethyl sulfoxide (DMSO). Working solutions were made by adding 4 mL of 10 N NaOH to 2.3 mL unbuffered normal saline (NS), and then adding 200 μL of glibenclamide or vehicle stock solution. The working solutions were then loaded into mini-osmotic pumps (Alzet 2001, 1.0 μl/h; Alzet Corp., Cupertino, CA). After loading, the mini-osmotic pumps were primed overnight in NS at 37 °C. This treatment results in a serum glibenclamide concentration of ~5 ng/mL, which minimally impacts serum glucose [14].

For glibenclamide pre-treatment, at 7 days prior to dc-bTBI, rats were given a glibenclamide loading dose of 10 μg/kg intraperitoneally. At this time, pumps calibrated to deliver 200 ng/hour of glibenclamide over 7 days were loaded with either glibenclamide or vehicle and implanted subcutaneously under general anesthesia. In these rats, immediately following bTBI one week later, the previously implanted pumps were removed and replaced with freshly prepared pumps that were also calibrated to deliver 200 ng/hour of glibenclamide over 7 days.

For glibenclamide post-treatment, immediately following bTBI, rats were given a glibenclamide loading dose of 10 μg/kg intraperitoneally. At this time, pumps calibrated to deliver 200 ng/hour of glibenclamide over 7 days were loaded with either glibenclamide or vehicle and implanted subcutaneously under general anesthesia.

2.3. Physiological measurements

All rats underwent continuous pulse oximetry and heart rate recordings (Mouse Ox; STARR Life Sciences Corp., Oakmont, PA). Readings were obtained at baseline, and continuously for 30 min after dc-bTBI.

2.4. Blood-brain barrier permeability

BBB permeability was quantified by spectrophotometric measurement of Evans blue extravasation [32]. BBB permeability was assessed at 5 min, 15 min, 3 h and 24 h after dc-bTBI. Briefly, under general anesthesia, Evans blue was introduced via a tail vein catheter (Braintree Scientific, Braintree, MA) at a concentration of 50 mg/kg and allowed to circulate for 60 min. To standardize the time that Evans blue was present in circulation, Evans blue was injected 55 and 45 min before dc-bTBI in the 5 and 15 min groups, whereas Evans blue was injected 2 h and 23 h after dc-bTBI in the 3 h and 24 h groups.

Rats were euthanized by intracardiac perfusion with normal saline, and brains were harvested and divided into the cerebrum, and cerebellum. The specimens were weighed, covered separately in aluminum foil and dried in an oven for 2 days at 56 °C. After 2 days, the dry weights were measured. Formamide (8 mL/gm of dry tissue) was added to each sample, and samples were returned to an oven at 56 °C for an additional 2 days. The supernatant was collected and centrifuged at 13,200 rpm. Absorbance was detected at 620 nm with a spectrometer (Spectronic BioMate3; Thermo Fisher Scientific Inc., Waltham, MA). For each experiment, Evans blue standards were prepared (0, 0.25, 0.5, 1, 2, 4, and 8 μg/mL) in formamide. Background absorbance was assessed with naïve rat brain tissue. Control Evans blue extravasation was assessed by infusing Evans blue into sham-injured rats.

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