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Plenary article

Attenuation of interleukin-1beta by pulsed electromagnetic fields after traumatic brain injury

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ABSTRACT

Traumatic Brain Injury (TBI) is a major cause of morbidity and mortality in civilian and military populations. Interleukin-1beta (IL-1β) is a pro-inflammatory cytokine with a key role in the inflammatory response following TBI and studies indicate that attenuation of this cytokine improves behavioral outcomes. Pulsed electromagnetic fields (PEMF) can reduce inflammation after soft tissue injuries in animals and humans. Therefore, we explored whether PEMF signals could alter the course of IL-1β production in rats subjected to closed-head contusive weight-drop injuries (Marmarou method) and penetrating needle-stick brain injuries. Protein levels, measured by the Biorad assay, were not altered by injuries or PEMF treatment. In addition, we verified that IL-1β levels in cerebrospinal fluid (CSF) were proportional to injury severity in the contusion model. Results demonstrate that PEMF treatment attenuated IL-1β levels up to 10-fold in CSF within 6 h after contusive injury and also significantly suppressed IL-1β within 17–24 h after penetrating injury. In contrast, no differences in IL-1β were seen between PEMF-treated and control groups in brain homogenates. To the authors' knowledge, this is the first report of the use of PEMF to modulate an inflammatory cytokine after TBI. These results warrant further studies to assess the effects of PEMF on other inflammatory markers and functional outcomes.

1. Introduction

Approximately 1.7 million people are treated annually in the U.S. for the neurological and physiological deficits resulting from TBI, a leading cause of death under the age of 45 [7,28]. Head injuries induce a cascade of molecular, cellular, and vascular responses to produce brain inflammation and swelling. If allowed to continue unchecked, these processes can lead to neuronal death and cognitive impairment [4,8,35]. Despite promising pre-clinical data and early phase trials, no intervention has convincingly demonstrated clear benefits in terms of improving long-term outcome after TBI in humans [17].

Although the CNS was once considered an "immune privileged" site [20], it is now clear that the brain will mount a robust and long-lasting inflammatory response to injury [4,35]. IL-1β is a pro-inflammatory cytokine and major upstream mediator of the post-traumatic inflammatory response. In humans, IL-1β levels in CSF have been correlated with high intracranial pressure and unfavorable outcomes [27]. IL-1β is not thought to cause neuronal injury directly, but rather, this cytokine may act through astrocytes [24] responding to noxious stimuli [34]. For example, injections of IL-1β exacerbated the breakdown of the blood–brain barrier after middle cerebral artery occlusion [19]. Intracerebroventricular injections of IL-1β resulted in necrosis, edema and inflammation following TBI in the rat [12]. Conversely, neutralization of IL-1β resulted in significant reductions of TBI-induced brain necrosis, suggesting that IL-1β contributes to neuronal death [5,26]. Therefore, it is possible that suppressing IL-1β induction after TBI will increase neuronal survival.

PEMF signals have demonstrated clinical success for the treatment of recalcitrant bone fractures [9], soft-tissue injuries [14], post-surgical pain [25], and inflammation-induced edema [22]. Importantly, PEMF signals can also modulate cytokine production. In a recent clinical study, PEMF therapy produced 3-fold reductions in IL-1β concentrations in surgical wound exudates post-operatively [25]. Because of the key role of IL-1β as an early responder to injury, an inducer of the pro-inflammatory response, and a predictor of clinical outcome after TBI, we examined and characterized the effects of PEMF signals on IL-1β in rats after closed-head or penetrating injuries.

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2. Materials and methods

2.1. Animals

Adult male Sprague Dawley rats (350–400 g) were housed in a climate-controlled animal facility with two rats per cage. Food and water were provided ad libitum in a 12-h light/dark cycle. Animals were maintained, operated on, treated, and euthanized in accordance with federal, state, and IACUC guidelines at the Montefiore Medical Center. Rats were randomly assigned into treatment groups as follows: intact (no procedure), sham (surgery without head injury), null (surgery, head injury, no PEMF treatment), and PEMF (surgery, head injury, PEMF treatment).

2.2. Closed-head contusion injury

Rats were subjected to a moderate closed-head injury under anesthesia using the Marmarou impact-acceleration model [18]. Rats were anesthetized with ketamine/medetomidine (75 mg/0.5 mg/kg, i.p.). After depilation and disinfection, the *calvarium* was exposed by creating a 1 cm vertical, midline scalp incision and displacing the *periosteum*. To diffuse the impact force and reduce the incidence of skull fracture, a metal washer (10 mm diameter, 2 mm thickness) was affixed to the skull with epoxy midway between lambda and bregma. Rats were secured directly underneath the weight-drop device on foam bedding (Foam to Size; Ashland, VA; spring constant = 4.0). A diffuse closed-head injury was produced by dropping a 237-g weight in a plastic cylinder from specified heights up to 2 m, creating impact energy from 1 to 4 J. After impact, the washer was removed from the skull and the *periosteum* and scalp were approximated with interrupted nylon sutures. Anesthesia was reversed with 1 mg/kg atipamezole and animals in the PEMF group were exposed to PEMF signals. Animals in the null group (no signal) were handled similarly. CSF was collected under anesthesia at 6 h after injury, when IL-1β induction was predicted to increase for this type of injury [15]. After euthanasia, cerebral hemispheres were collected in plastic wrap and frozen immediately in a −80 °C freezer for subsequent processing.

2.3. Penetrating brain injury

Rats were anesthetized (see above) and secured on a stereotaxic frame (David Kopf) with the tooth bar at 3.3 mm below the interaural line. After depilation and disinfection, the *calvarium* was exposed and the separated tissue was secured with hemostats. Two 1-mm burr holes were created by a trephine drill above each *striatum* at stereotactic coordinates 0.5 mm anterior to and 2.5 mm lateral to bregma. A 23S gauge blunt-end needle from a Hamilton syringe was inserted 5.2 mm below the dura and then removed. Burr holes were sealed with bone wax and the incision site was closed. Rats were reversed from anesthesia, randomized to PEMF and null treatment groups, and treated for specified times. Prior to euthanasia, CSF was collected and after euthanasia, 5-mm cylinders of tissue around the left-side lesion were collected in plastic wrap, frozen immediately in a −80 °C freezer, and subsequently processed for quantification of IL-1β by ELISA.

2.4. PEMF treatment

Animals assigned to the PEMF group were exposed to a 27.12 MHz radio frequency carrier pulse-modulated signal with a 3 ms burst repeating at 2 Hz (Ivivi Health Sciences, San Francisco, CA). A single-turn coil positioned mid height around a rectangular plastic container (4″W × 8″L × 4″H) with a ventilated lid permitted a single rat to be uniformly (±20%) exposed such that the mean induced electric field within the brain was 40 ± 6 V/m. PEMF was applied in a continuous regimen of 5 min in every 20 min for 6 h. For treatments longer than 6 h, rats were placed in their original cage with plastic ventilated covers and metal inserts removed. Food and hydrogel packs were provided. Cages were placed within a larger plastic container wrapped with a 14″ × 28″ single-turn coil 6″ above the bottom on a plastic cart in the animal facility to avoid signal distortion from surrounding metal. The PEMF treatment regimen was set at 5 min in every 20 min for up to 9 days starting immediately following injury. Identical procedures were followed for the null group.

2.5. CSF collection

CSF was obtained utilizing a modification of the Nirogi technique [21]. A 23G Vacutainer® push-button blood collection needle with 12-in. tubing (BD) was connected to a 1 cc insulin syringe. Anesthetized rats were positioned on a stereotaxic frame with the tooth bar angling the head 45° in a downward direction. The needle was inserted vertically into the medial portion of the *cisterna magna* until CSF was released into the tubing. Fluid was collected until blood was visible and tubing was clamped to separate clear and blood-tainted CSF. Clear CSF was released into microfuge tubes and cellular material was pelleted by centrifugation at 4000 × *g* for 4 min at 4 °C. Cleared samples were immediately frozen at −80 °C.

2.6. Tissue processing

For weight-drop and penetrating injuries, whole brain hemispheres minus cerebella or 5-mm cylinders of brain tissue surrounding the stab injury, respectively, were used. Frozen specimens were homogenized using a polytron (VirSonic 300, Virtis) in lysis buffer containing tris-buffered saline (TBS; 10 mM trizma base, 140 mM sodium chloride, pH 7.4) with 2 mM EGTA, 1 mM sodium orthovanadate, 10 mM sodium fluoride, and complete mini protease-inhibitor tablets (Roche) and centrifuged at 16,000 × *g* for 10 min at 4 °C to pellet particulate matter. Supernatants were frozen at −80 °C and Triton X-100 was added to a final concentration of 0.1% before assays.

2.7. IL-1β analysis

IL-1β levels were quantified on duplicate samples using a rat IL-1β enzyme-linked immunosorbant assay (ELISA) (R&D Systems duo set; capture antibody 1:100). Mean data for brain homogenates were normalized for protein content determined with the Biorad protein assay.

2.8. Statistical analysis

Data were analyzed by ANOVA followed by the Fisher PLSD test. Statistical significance was accepted for p-values ≤ 0.05. Data are expressed as mean values ± standard errors of the mean (SEM).

3. Results

3.1. Levels of IL-1β in CSF are proportional to impact force

Experiments were conducted to examine the relationship between injury severity and IL-1β induction after closed-head injury (Fig. 1a). Animals were divided into three groups (intact ($n = 5$), sham ($n = 5$), and injured ($n = 40$)). Injured rats were subjected to contusive injuries ranging from 1 to 4 J ($n = 10$/group). Six hours after injury, CSF was collected and IL-1β levels were quantified by ELISA. IL-1β concentrations in CSF ranged from 19

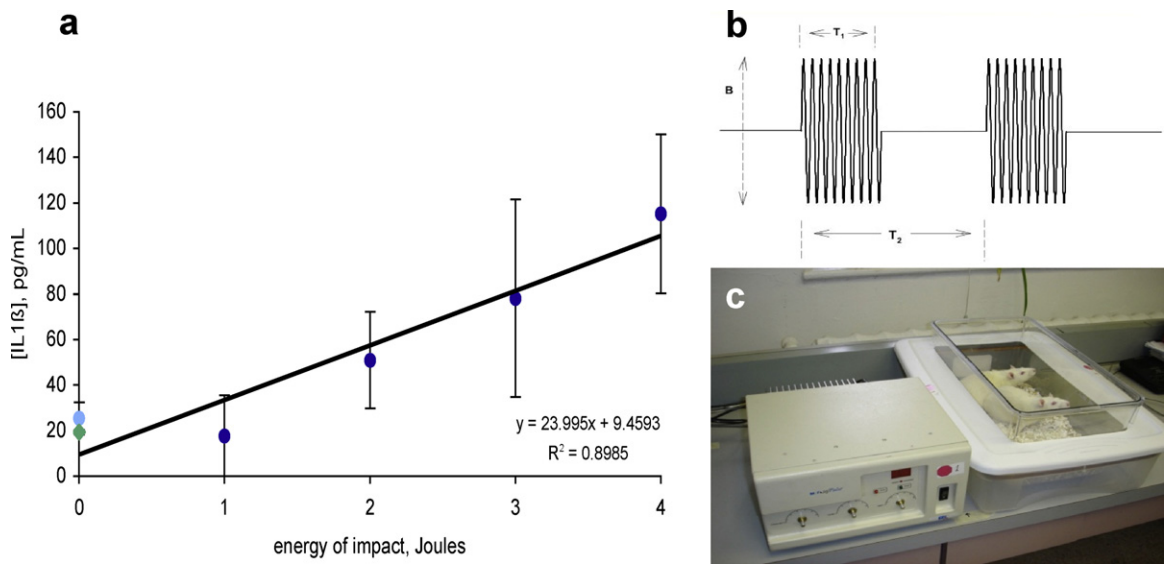

Fig. 1. Initial parameters of injury, PEMF signal configuration, and treatment regimen. (a) [IL-1β] in CSF is proportional to the energy of impact after contusive injuries. Rats were subjected to a contusive weight-drop injury and sacrificed at 6 h. CSF was collected from animals in intact ($n = 5$, green), sham ($n = 5$, light blue), and injured ($n = 10$, dark blue) groups and processed for quantification of IL-1β by ELISA. IL-1β concentrations correlated closely with the energy of impact ($R^2 = 0.8985$). Bars represent mean [IL-1β] ± SEM. (b) PEMF signal: 27.12 MHz sinusoidal carrier, pulse modulated with a 5 ms burst (T_1), repeating at 2 bursts/s (T_2), inducing a peak magnetic field ($B = 0.05$ G) inducing a mean of 40 V/m peak electric field in situ. This PEMF signal is non-thermal and does not produce excitable membrane activity. (c) PEMF treatment regimen. Rats in standard cages were placed within a plastic box fitted with a coil around its perimeter. Signals were applied using a Sofpulse generator programmed to deliver PEMF for 5 min every 20 min. Animals in the null group were treated in an identical manner in the absence of PEMF signals.

to 115 pg/mL, which correlated closely with the energy of impact ($R^2 = 0.8985$).

3.2. PEMF treatment reduced levels of IL-1β in CSF after contusive TBI

Rats were subjected to contusive injuries and randomly assigned to PEMF and null treatment groups (Fig. 1b and c). Results demonstrate that IL-1β concentrations in CSF increased significantly in response to injury (Fig. 2a). Mean IL-1β concentrations in CSF were 19 ± 7 pg/mL for intact animals and 25 ± 21 pg/mL for the sham group. IL-1β concentrations in CSF for the null group rose to 262 ± 91 pg/mL, a 10-fold increase over the sham and intact groups ($p \leq 0.05$). In contrast, animals treated with PEMF signals had 5-fold lower IL-1β concentrations (44 ± 25 pg/mL) than those of the null group ($p \leq 0.02$), and were not significantly different from the sham and intact groups.

Brain homogenates of intact animals had the lowest levels of IL-1β (29 ± 4 pg/mg protein), followed by the sham group (39 ± 7 pg/mg protein) (Fig. 2b). The mean IL-1β concentration in the null group was 55 ± 3 pg/mg protein, a significant increase over intact (89%; $p \leq 0.0002$) and sham (41%; $p \leq 0.03$) groups, albeit to a lesser extent than in CSF. IL-1β increased in homogenates in the PEMF group to 50 ± 4 pg/mg protein, a 72% increase over the intact group ($p \leq 0.002$), but there was no significant difference between null and PEMF groups.

3.3. PEMF reduced levels of IL-1β after penetrating brain injury

To investigate the effects of PEMF treatment on IL-1β induction in more invasive injuries, rats were randomized into null and PEMF groups and subjected to a penetrating needle injury that produced a focal inflammatory response. CSF ($n = 4$–6) and brain tissue surrounding the injury ($n = 5$–16) were collected at specified times up to 9 days. In CSF (Fig. 2c), basal levels of IL-1β in intact animals were 32 ± 32 pg/mL (green dot). Levels in the null group stayed low at 6 h after injury, but rose to reach a maximum of 224 ± 23 pg/mL at 17 h, a 7-fold increase over basal levels ($p \leq 0.001$). In contrast, PEMF-treated animals maintained basal levels of IL-1β throughout the experiment. Importantly, levels of IL-1β in the PEMF group were approximately 10-fold lower than the null group at 17 h after injury (23 ± 18 pg/mL vs. 224 ± 23 pg/mL, $p \leq 0.001$). Concentrations of IL-1β remained high in the null group at 24 h (122 ± 56 pg/mL), continued to be lower in the PEMF group (31 ± 16; $p \leq 0.015$), and decreased to baseline levels at 5–9 days after injury (31–45 pg/mL). IL-1β concentrations were lowest in both treatment groups at 9 days (0–3 pg/mL). Together, results demonstrate that PEMF treatment suppressed the increase in IL-1β levels in CSF at 17–24 h after penetrating injury.

In brain homogenates, basal IL-1β concentrations for intact animals were 24 ± 5 pg/mg protein (Fig. 2d; green dot). Maximal levels of IL-1β were attained at 6 h after injury for both PEMF (99 ± 11 pg/mg protein) and null (93 ± 15 pg/mg protein) groups. Although at 17 h after injury IL-1β levels appeared lower in the PEMF group (42 ± 6 pg/mg protein) compared to the null group (61 ± 5 pg/mg protein), these values were not significantly different.

4. Discussion

Due to the growing number of soldiers, athletes, and civilians who are victims of TBI and the lack of an effective treatment to prevent the consequences of secondary injuries, new strategies to minimize neuronal loss are urgently needed. Despite the important role of the inflammatory response in healing damaged tissue, prolonged inflammation can establish feed-forward loops that may overwhelm normal resolution mechanisms and ultimately lead to poor outcomes. Corticosteroids, which reduce edema and inflammation, were shown to increase morbidity and mortality in humans after TBI [6], possibly due to systemic stress and neurotoxicity. Therefore, novel therapies designed to selectively and specifically reduce inflammation are attractive.

Our results indicate that expression of IL-1β in brain homogenates and CSF are consistent with those of other groups [15,27]. Interestingly, IL-1β was also detectible in intact and sham-operated animals, albeit at lower levels. This may be due to

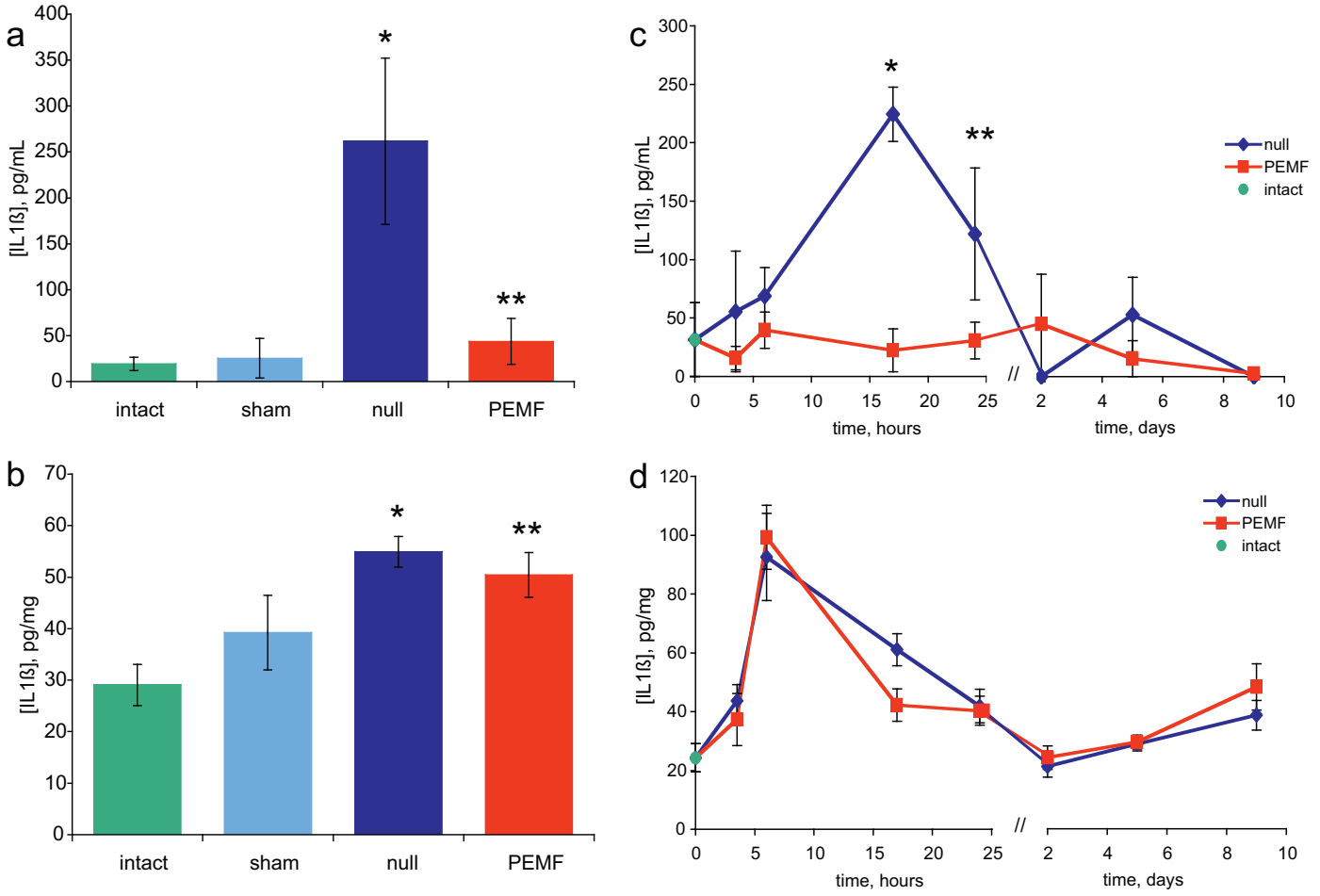

Fig. 2. PEMF signals reduced IL-1β in CSF after TBI. IL-1β induction in rats subjected to closed-head or penetrating needle injury was quantified by ELISA in CSF (a, c) and brain homogenates (b, d). Bars represent mean [IL-1β] ± SEM, with asterisks indicating significant differences between groups ($p \leq 0.05$). (a) Closed-head injury, 6 h, CSF: $^{*}p \leq 0.05$, null vs. intact or sham; $^{**}p \leq 0.02$, PEMF vs. null and not significantly different than intact or sham ($p = 0.472$). (b) Closed-head injury, 6 h, homogenates: $^{*}p \leq 0.0002$ null vs. intact and ≤ 0.03 null vs. sham. $^{**}p \leq 0.002$ PEMF vs. intact. (c) Penetrating injury, CSF, time course: IL-1β in CSF for the null group was significantly higher than the PEMF group at 17 ($^{*}p \leq 0.001$) and 24 ($^{**}p \leq 0.015$) h after injury. (d) Penetrating injury, brain homogenates, time course: no significant differences in IL-1β were found between treatment groups at any time point.

infiltration of systemic inflammation produced by sham surgery or non-mechanical stress due to transport, injection of anesthesia, or new surroundings, as psychological stress has been shown to elevate IL-1β [2]. Importantly, increases in IL-1β levels after injury were more pronounced in CSF than in homogenates. It should be noted that IL-1β is synthesized as a precursor protein that is cleaved by caspase-1 to produce its active extracellular form [1,30]. While the ELISA recognizes both forms in brain tissue, increases due to injury represent only a fraction of the total IL-1β. However, the active form is released into the extracellular space, which communicates freely with CSF, even though CSF levels can differ from extracellular concentrations, as demonstrated in microdialysis studies [11]. Nevertheless, the majority of IL-1β in CSF should at least reflect relative amounts of the active form released after injury, which may also explain why peak IL-1β levels in brain homogenate precede those in CSF. Thus, CSF appears to be superior to brain homogenates for monitoring and quantifying IL-1β in animal models.

In humans, higher levels of IL-1β after TBI correlate with unfavorable outcomes [27], suggesting that PEMF treatment may be beneficial by suppressing its expression and/or activation. This hypothesis is consistent with other studies in a variety of brain injury models [5,10,13,29,31]. In these studies, the degree of IL-1β suppression ranged from 30% to 65%. In contrast, our study demonstrated up to 90% reductions in IL-1β, which could increase the magnitude of positive outcomes.

Recent work provides clues to understanding the mechanism of action of the PEMF signal used in this study and proposes that it can increase calmodulin-dependent nitric oxide (NO) synthesis [23], leading to the possibility that some of the effects of PEMF observed in this study were mediated by NO. Because NO can inhibit caspase-1 activity [16], PEMF may prevent caspase-1 from releasing active IL-1β, which is consistent with our data indicating that the magnitude of IL-1β induction and PEMF effects were higher for CSF than for brain homogenates. It should also be noted that NO is a vasodilator, which could be beneficial after TBI, however, it can also form peroxynitrite which can adduct to proteins, compromising their activity [3]. Studies of other PEMF signal configurations suggest that neuronal and immune effects may be mediated by altering adenosine receptor levels [32,33], but the mechanism that accounts for these changes is unknown.

In summary, we demonstrate that PEMF therapy successfully suppressed the induction of IL-1β in two models of TBI in rats. Therefore, it is possible that this type of therapy will improve

outcomes after brain injury in humans. Additional studies examining the effect of PEMF signals on neuronal survival and neurological outcomes after TBI are warranted.

Disclosure statement

A.A.P. receives compensation as a scientific consultant to Ivivi Health Sciences. A.A.P., D.C. and B.S. may receive a small royalty from Ivivi Health Sciences if a recent TBI patent disclosure issues and Ivivi is able to commercialize a TBI product.

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