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Implication of surgical procedure in the induction of headache and generalized painful sensation in a fluid percussion injury model in rats

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ABSTRACT

Background: This study demonstrated the effects of traumatic brain injury (TBI) and each step of the surgical procedure for a fluid percussion injury (FPI) model on periorbital allodynia.
New method: Adult male Wistar rats were divided in naive, incision, scraping, sham-TBI and TBI groups. Periorbital allodynia was evaluated using von Frey filaments, and heat hyperalgesia of the hindpaws was evaluated by a Plantar Test Apparatus.
Results: The statistical analyses revealed that the surgical procedure decreased von Frey filaments thresholds twenty-four hours after the surgery in all groups when compared to the naive group ($p < 0.0001$). Scraping, sham-TBI and TBI groups showed a decrease in the periorbital mechanical threshold for 35 days compared with the naive and incision groups ($p < 0.0001$). Only the TBI group demonstrated a significant difference in periorbital allodynia at 45 and 60 days after the injury ($p < 0.01$). A significant decrease in the thermal withdrawal latency of the hindpaw contralateral to the lesion was observed in the TBI group compared with the naive group at 7 days and 28 days after the lesion ($p < 0.05$).
Comparison with existing methods: This study presented in detail the effects of each stage of the surgical procedure for a FPI model on periorbital allodynia over time and characterized the TBI model for this evaluation.
Conclusion: The FPI model is relevant for the study of headache and generalized pain in both acute and chronic phases after an injury.

1. Introduction

Traumatic brain injury (TBI) is a condition that often results in death and disabilities in both civilian and military populations, where the majority of TBI survivors suffer from subsequent lifelong neurological symptoms, such as post-traumatic headache (PTH). It is estimated that PTH after brain damage occurs in 30–90% of patients (Hoffman et al., 2011; Lucas, 2011) and persists for months or years after the lesion (Lucas et al., 2014).

In this sense, some TBI models have been used to evaluate periorbital allodynia in mice and rats (Daiutolo et al., 2016; Elliott et al., 2012; Macolino et al., 2014; Tyburski et al., 2017; Wang et al., 2017). For example, the painful sensations caused by an innocuous stimulus in the periorbital region of mice after controlled cortical impact (CCI) involves the activation of the trigeminal system. At a cellular level, nociceptive neuropeptide release, namely, calcitonin gene-related peptide (CGRP) and substance P (SP), increases from primary neurons in the dura mater, and the cerebral system reduces the thresholds for periorbital allodynia after a craniectomy and a TBI (Elliott et al., 2012). These same TBI model also induce bilateral periorbital allodynia up to one month after the injury (Macolino et al., 2014).

Recently, it has been demonstrated that closed head injury in rats using an electromagnetic device, where a midline incision was made to expose the skull and the bregma, is able to induce trigeminal sensitivity (Tyburski et al., 2017). In this report, a modified 10-mm diameter rubber impactor tip was used to deliver the lesion, for which the velocity and dwell time were held constant at 5 m/s and 100 milliseconds, respectively. The authors suggest that trigeminal sensitivity in this study was dependent on the frequency of injuries and recovery time between injuries, considering that no fractures to the skull or intracranial bleeding were observed. Moreover, some characteristics, such behavioral and histopathological changes, in rats were indicative

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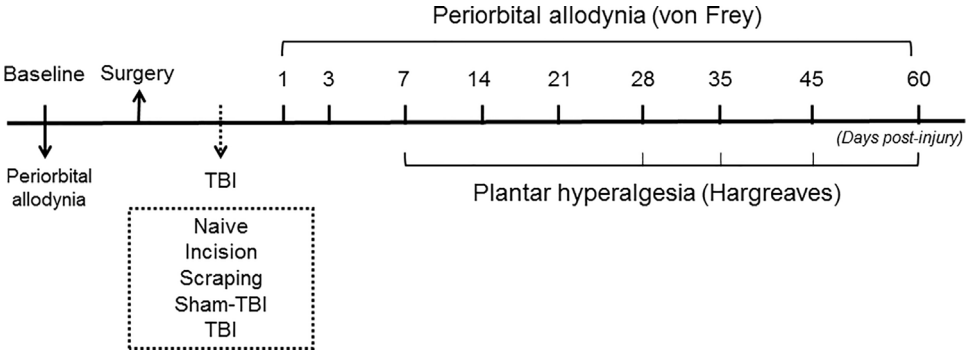

Fig. 1. Timeline of the experimental procedures for traumatic brain injury, periorbital allodynia and hyperalgesia thermal characterization.

of a post-concussion headache (Tyburski et al., 2017). Another closed head injury model used for PTH is a weight-drop device. In this model of neurological injury, the skull is exposed to a free-falling guided weight, and injury severity can be altered by adjusting the mass of the weight and the height from which it falls (Morales et al., 2005). The weight-drop device induces cephalic tactile pain hypersensitivity in rats, with a mild injury in the acute phase after neuronal injury and improvements in the two weeks post-injury (Bree and Levy, 2016).

Under pathological conditions after TBI, peripheral sensitization can occur, resulting from changes in the neuronal activation, increase of the excitability of central nervous system (CNS) (Sommer and Kress, 2004) and maladaptive pain states (Old et al., 2015), that consequently lead to hyperalgesia and allodynia (Sommer and Kress, 2004). Similar to a migraine, cephalic tactile allodynia is thought to be a consequence of inflammatory-related activation and sensitization of trigeminal system (Burstein et al., 2000). In this line thinking, it was demonstrated that lesion in mice by fluid percussion injury (FPI) model can leads to inflammation peripheral and cause an disturbance in regulatory T cells (Rowe et al., 2016).

Although the FPI model is one of the most widely used TBI animal models (Thompson et al., 2005) and recreates the etiological processes that induce TBI in humans (Alder et al., 2011), there are several critical steps to consider in order to increase the validity and reliability of this technique. For example, it is important that only animals in which the integrity of the dura has not been compromised during the craniectomy be subjected to FPI. Considering that craniectomy also results hypersensitivity and neuroinflammation (Cole et al., 2011; Elliott et al., 2012; Flexman et al., 2010), this procedure in FPI control animals (usually craniectomy) could confound the results found for painful sensations in the head region. However, these ideas are speculative, and conclusive studies are necessary to clarify the occurrence of PTH elicited by this model of neurological injury.

In this sense, we resolved to investigate painful sensations in rats after FPI by characterizing the acute and chronic phases of a headache and the widespread pain after TBI. To verify whether the surgery to create a FPI model can induce a headache, we also evaluated the effect of the surgical procedure on periorbital allodynia. For a better characterization of the painful sensations in the FPI model, we also evaluated hindpaw pain thresholds in order to verify if the induced lesion is capable of affecting pain distant from the lesion site from a thermal stimulus and if this sensitivity remains for a long period.

2. Materials and methods

2.1. Animals

This study used adult male Wistar rats (2.5–3 months of age at the time of the intervention) (250–350 g). The animals were maintained in a ventilated rack, and each group had of a maximum of 3 animals per box, which measured 27 × 26 × 31 cm and was covered by shavings; animals were maintained under a controlled light environment (12:12 h light-dark cycle, 22 ± 2 °C, 55% relative humidity), with ad libitum access to standard laboratory diet (BioBase®, Águas Frias, SC, Brazil) and water [filtered for fecal coliform and heavy metals (Jojaco®, model J190, Capivari de Baixo, SC, Brazil)]. All procedures with animals followed guidelines of the Committee on Care and Use of Experimental Animal Resources of the Federal University of Santa Catarina (protocol number 2712080317).

2.2. Experimental design

The animals were habituated over three consecutive days (5 min/day) to the behavior testing Von Frey sensory (mechanical allodynia) apparatus and afterwards underwent baseline assessments. Twenty-four hours after the baseline assessment, a surgical procedure was performed for the implantation of the TBI cannula. Animals were randomly assigned to naive (no procedure), incision (longitudinal skin incision and suture), scraping (incision, scraping of skull for removal of calvarial periosteum overlying the frontal and parietal bones and suture), sham-TBI (incision, scraping of skull, craniectomy for implantation of the TBI cannula and suture) or TBI (all procedures and fluid impact) groups. All these groups were created to verify the painful effect of each procedure performed in the surgery and only the impact of fluid on the brain through a periorbital allodynia test after the TBI over time (1, 3, 7, 14, 21, 28, 35, 45 and 60 days after the lesion). Concomitantly, three of these groups (naive, sham-TBI and TBI) underwent assessments of hindpaw hyperalgesia over time (7, 28, 35, 45 and 60 days after the lesion) (Fig. 1).

2.3. Surgical procedure and induction of a parasagittal TBI model

The FPI was conducted as previously described (Fiorin et al., 2016). Briefly, animals were anesthetized with a single intraperitoneal injection of Equithesin (6 mL/kg), a mixture of sodium pentobarbital (58 mg/kg), chloral hydrate (60 mg/kg), magnesium sulfate (127.2 mg/kg), propylene glycol (42.8%), and absolute ethanol (11.6%), and placed in a rodent stereotaxic apparatus. A unilateral burr hole with a 3-mm diameter was drilled into the right convexity over the parietal cortex (2 mm posterior to bregma and 3 mm lateral to midline); close attention was paid to maintain an intact dura mater. A plastic injury cannula was cemented into the craniectomy with dental cement. When the dental cement hardened, the cannula was filled with saline and closed with a proper plastic cap; by this time, the animal had been removed from the stereotaxic device and returned to its home cage. After 24 h, the animals were anesthetized with isoflurane (1% inhaled), and the injury cannula was attached to the fluid percussion device. A fluid percussion apparatus developed in our laboratory produced the FPI. A brief transient pressure fluid pulse impact was applied to the exposed dura. For the present study, the FPI device was adjusted to consistently deliver similar injury severity parameters (apnea,