Lasers in Medical Science (2019) 34:1841–1847
https://doi.org/10.1007/s10103-019-02785-6

ORIGINAL ARTICLE

Photobiomodulation-induced analgesia in experimental temporomandibular disorder involves central inhibition of fractalkine

João Ignácio Ferrara-Jr[1] · Everton Tiago de Souza[1] · Adriano Cardozo Franciosi[1] · Elaine Flamia Toniolo[1,2] · Camila Squarzoni Dale[1]

Received: 5 September 2018 / Accepted: 3 April 2019 / Published online: 10 April 2019

Abstract

Temporomandibular disorder (TMD) is a collective term that encompasses a set of clinical problems that affect the masticatory muscles, the temporomandibular joint, and associated structures. Despite their high clinical prevalence, the mechanisms of chronic craniofacial muscle pain are not yet well understood. Treatments for TMD pain relief and control should be minimally invasive, reversible, and conservative. Photobiomodulation (PBM) is a promising option once it is known to inhibit inflammatory response and to relief painful symptoms. Herein, the effects of PBM (660 nm, 30 mW, 16 J/cm^2, 0.2 cm^2, 15 s in a continuous frequency) on the pain sensitivity of rats submitted to an experimental model of TMD induced by CFA was evaluated. Experimental TMD was induced in rats by the injection of complete Freund's adjuvant (CFA) injection into the masseter muscle. Nociceptive behavior was evaluated by electronic von Frey before CFA and after 1 h, 3 h, 6 h, and 24 h and 7, 14, and 21 days after PBM treatment. Inflammatory infiltrate was evaluated by histology of the masseter muscle and fractalkine expression was evaluated by immunohistochemistry of the trigeminal ganglia. PBM reversed the mechanical hypersensitivity of the animals by inhibiting the local inflammatory response, observed by the decrease of the inflammatory infiltrate in the masseter muscle of rats and by a central inhibition of fractalkine observed in the trigeminal ganglion. These data provide new insights into the mechanisms involved in the effects of photobiomodulation therapy emphasizing its therapeutic potential in the treatment of TMD.

Keywords Photobiomodulation · Orofacial pain · Microglia · Fractalkine · Inflammation

Introduction

Temporomandibular disorders (TMD) is a general term that comprises a wide range of clinical problems involving the masticatory musculature, the temporomandibular joint (TMJ), and its associated structures. Clinical signs and symptoms include the following: impaired jaw movement capacity, tenderness upon palpation of the TMJ, and the masticatory muscles and pain [1]. Epidemiological studies have obtained conflicting results regarding the prevalence and incidence of TMD; however, studies indicate that those of muscular origin are more prevalent [2–5]. In spite of its high clinical prevalence, the mechanisms of chronic craniofacial muscle pain are not well understood and experimental studies suggest that inflammation may play the potential roles in these disorders [6, 7].

Initial therapeutic options for TMD pain relief and control should be minimally invasive, reversible, and conservative. In this context, several studies have shown that photobiomodulation (PBM) therapy can be considered a useful tool in the treatment of TMDs [8–10]. Clinical trials have demonstrated that PBM is efficient in treating TMD, emphasizing significant remission and relief of painful symptoms [11–17]. Thus, considering that TMD is one of the most prevalent conditions of orofacial pain, especially those of muscular origin, in which varieties of theories related to etiology are

✉ Camila Squarzoni Dale
camila.dale@usp.br

[1] Laboratory of Neuromodulation of Experimental Pain, Department of Anatomy, Insitute of Biomedical Sciences, University of São Paulo, Av. Professor Lineu Prestes 2415, ICB III, Cidade Universitária, Sao Paulo 05508-900, Brazil

[2] University City of São Paulo, Campus of Pinheiros, Rua Butantan, Sao Paulo 05425-140, Brazil

glimpsed, and that the current therapeutic modalities are presented as refractory, uncomfortable and unsatisfactory, it is necessary to establish appropriate therapy for pain relief, making PBM a promising option as its effectiveness has been demonstrated in several studies. However, little is known about the mechanisms involved in its anti-inflammatory and antinociceptive effects.

Allying the experimental trials of microglial activation to orofacial pain models, considerable data indicate that glial cells play an important modulatory role in orofacial pain signaling pathways [18–23]. Fractalkine (CX3CL1), an inflammatory and pronociceptive chemokine, that has a unique connectivity to a single receptor, CX3CR1, present in the microglia [24–29] has been implicated in orofacial inflammatory pain [30, 31]. In this study, the effects of PBM, as well as the mechanisms involved were evaluated in experimental model of TMD in rats.

Materials and methods

Ethical aspects

Throughout the experiments, animals were managed using the principles and guidelines for the care of laboratory animals in studies involving pain and were approved by the Ethics Committee on the Use of Animals at University of São Paulo (CEUA, protocol no. 020/2014).

Animals

Adult male Sprague–Dawley rats (250–370 g), age matched, were used throughout this study ($n = 39$). Rats were maintained in a climate-controlled (22° ± 2 °C) and humidity-controlled (80%) room on a 12-h light/dark cycle with food and water available ad libitum. Animals were splitted in four groups: (1) control: animals injected with 100 μl of saline mixed with 100 μl mineral oil; (2) complete Freund's adjuvant (CFA): animals injected with 100 μl of CFA mixed with 100 μl saline 0.9%; (3) CFA+PBM On: animals injected with 100 μl of CFA mixed with 100 μl saline 0.9%, and treated with PBM; and (4) CFA+PBM Off: animals injected with 100 μl of CFA mixed with 100 μl saline 0.9%, and treated with PBM off. After the experiments, animals were euthanized and discarded according to routine laboratory procedures.

TMD experimental model

Rats were deeply anesthetized with intraperitoneal injection of ketamine hydrochloride (75 mg/kg)/xylazine hydrochloride (10 mg/kg) and under aseptic techniques, received an intramuscular injection of complete Freund's adjuvant emulsion (CFA; diluted in mineral oil solution, Sigma-Aldrich, St. Louis, MO). Each milliliter of CFA contains 1 mg of *Mycobacterium tuberculosis* that attracts macrophages and other cells to the injection site which enhances the immune response. Animals received 100 μl, of CFA solution that was mixed mixed with 100 μl saline 0.9%, 1:1, emulsified through three-way faucet, SOLIDOR™, Bio Med Health Care Products, Brazil), as suggested by the manufacturer, into the left masseter muscle between the zygomatic bone and the mandible angle [6]. Control group of animals received 100 μl, of mineral oil solution that was mixed mixed with 100 μl saline 0.9%, 1:1, emulsified as described before.

Assessment of orofacial mechanical sensitivity

Testing for mechanical sensitivity (von Frey, EFF 301, Insight, Ribeirão Preto/SP, Brazil) was based on the method of Denadai-Souza [32]. Rats were semirestrained manually, and transducer tip was applied on the left masseteric region with uniform and progressive force and velocity in order to obtain the smallest possible variation. Mechanical hyperalgesia of the face was evaluated by measuring the lowest strength intensity threshold, in grams, required for an animal's head withdrawal reflex. Head withdrawal measurements were repeated in triplicate at 5-min intervals. To reduce stress, rats were habituated to the experimental environment 2 days before the first measurement. All behavioral testings were conducted under blind conditions. The mechanical sensitivity measurements were accessed before CFA injection (day 0) and after 7, 14, and 21 days of CFA administration.

Light source, dose, and treatment

A low-level semiconductor indium gallium aluminum phosphorus (InGaAlP) (Photon Laser III, D.M.C., São Carlos, Brazil) emitting a wavelength of red 660 nm was used through the experiments with a beam spot of 0.2 cm^2 and an output power of 30 mW, energy density of 1.6 J/cm^2, and exposure time of 15 s in a continuous frequency. Laser doses, low enough to avoid any thermal effects, were chosen on the basis of previous studies from our group. Photobiomodulation sessions were performed with manually semirestrained animals on the same area that received CFA, for *either* 7 or 14 consecutive days.

Tissue processing and histology

At the end of the behavioral procedures, masseter samples from all evaluated animals were processed for histology, and hematoxylin–eosin staining was performed. Rats were irreversibly anesthetized and perfused with 0.1 M sodium phosphate buffer (PB; pH 7.4) followed by 4% paraformaldehyde (PFA) in 0.1 M phosphate buffer, pH 7.4. Left masseter

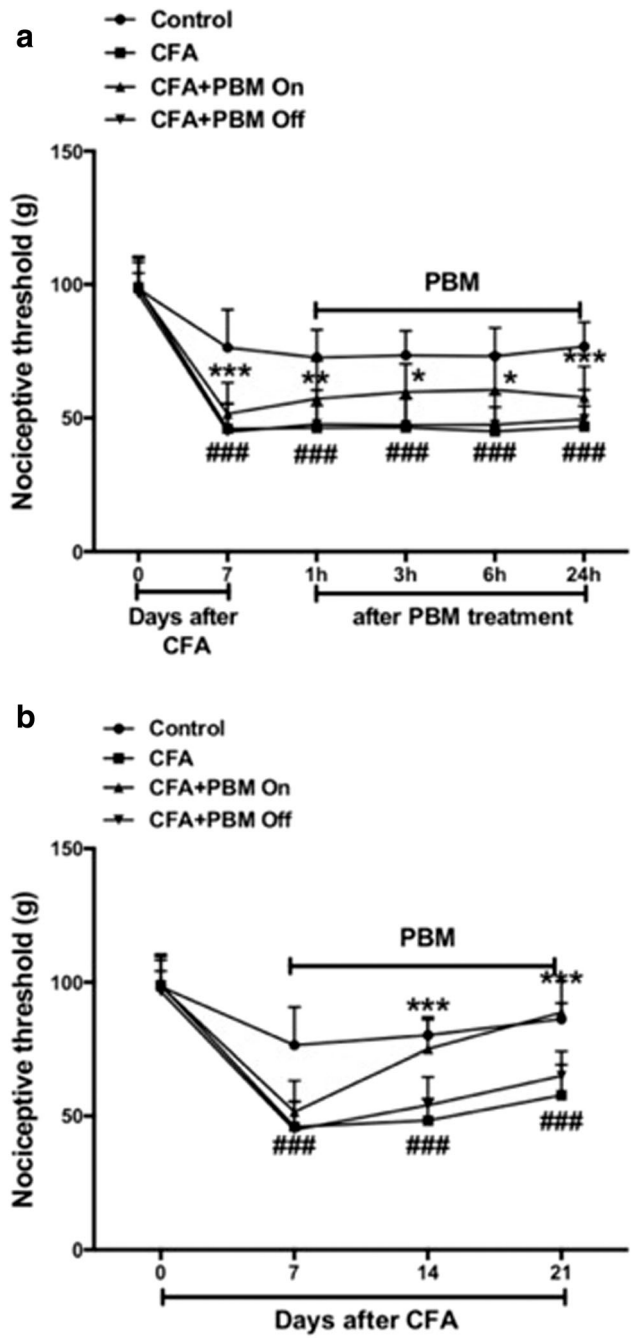

Fig. 1 Effect of PBM treatment on mechanical sensitivity of rats, evaluated by electronic von Frey. Animals were evaluated for mechanical sensitivity before any procedure (time 0), 7, 14, or 21 days after CFA. **a** On the 7th day, rats received the first application of PBM and were evaluated after 1 h, 3 h, 6 h, and 24 h of the first application. **b** Consecutive application of PBM was also evaluated after 7 and 14 applications. Groups of animals injected with vehicle (control) or injected with CFA or injected with CFA and treated with PBM Off were also evaluated. Data correspond to the mean ± S.E.M. of 6 to 11 rats per group. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, when comparing CFA and CFA+PBM On groups; $###p < 0.001$ when comparing CFA and control groups (two-way ANOVA, followed by the Bonferroni posttest)

muscle was excised, dissected, and postfixed in 4% PFA for 72 h and subsequently dehydrated in a gradual series of alcohol baths and then diaphonized with xylol for impregnation and inclusion of the samples in paraffin. Microtome cross-sections of 6 μm (Leica RM2125, Leica Biosystem, Germany) were transferred to histological silanized slides and examined by light microscope (Zeiss Axioskop 40, Germany), using either × 20 or × 40 objective. A qualitative analysis related to architectural characteristics, morphological alterations, inflammatory infiltrate, myonecrosis, and muscle regeneration was performed.

Immunohistochemistry

Samples from the left trigeminal ganglia were excised and dissected as described in item 2.5, postfixed in buffered 4% paraformaldehyde for 4 h, and cryoprotected in 30% sucrose solution. Serial transverse sections of 10 μm were cut with cryostat (Leica CM 1850, USA) and transferred to silanized slides and kept in − 20 °C. For the immunochemistry experiments, slides were washed in PB, 10 min, three times and incubated overnight with anti-IBAI (1:500, Millipore) or anti-CX3CL1(1:500, Affymetrix eBioscience, USA) primary antibodies, diluted in 0.3% Triton X-100 containing 50 μl of normal donkey serum. Following three washes of 10 min each with PB, sections were incubated for 2 h in the biotinylated secondary antibody (donkey anti-rabbit IgG, Jackson ImmunoResearch, PA, USA; 1:200), then in avidin–biotin complex (1:100; ABC Elite kit, Vector Labs, Burlingame, CA), and visualized using a mixture of 0.05% diaminobenzidine—0.01% hydrogen peroxide. Sections were then washed in PB, mounted on slides with a glycerol-based mounting medium, air-dried, dehydrated through graded ethanol solutions followed by xylene, and then coverslipped with Permount (Fisher Scientific, USA). Immunoreactivity was analyzed using a light microscope (Zeiss Axioskop 40, Germany), and the ImageJ 1.50i (Wayne Rasband, National Institutes of Health, USA) was used to perform quantitative analysis on the density of nuclei representative of the immunoreactivity for microglia (Iba-IR) or fractalkine (FKN-IR).

Statistical analysis

Results are presented as the mean ± standard error of the mean (SEM). Statistical analyses of data were generated using GraphPad Prism, version 6 (GraphPad Software Inc., San Diego, CA, USA). Statistical comparison of more than two groups was performed using analysis of variance (ANOVA) followed by Bonferroni's test. In all cases, $p < 0.05$ was considered statistically significant.

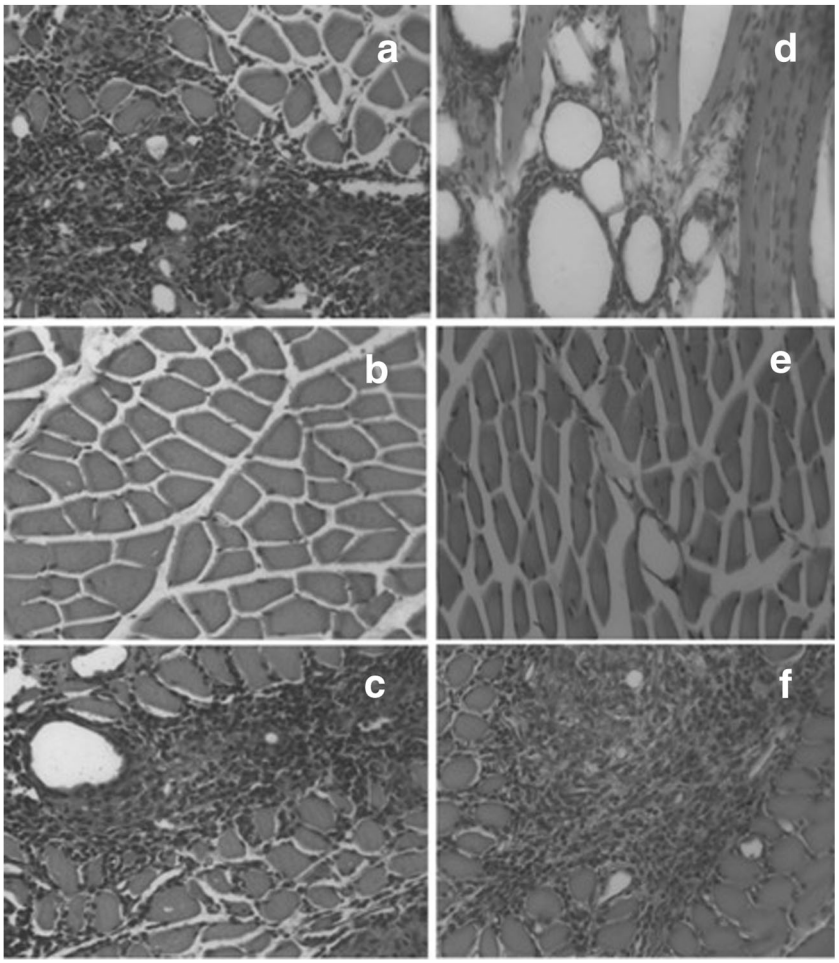

Fig. 2 Effect of PBM on morphological changes induced by CFA in the masseter of rats. Photomicrographs representative of the masseter muscle morphology of rats injected with CFA (**a**, **d**), CFA+PBM On (**b**, **e**), or CFA+PBM Off (**c**, **f**) groups after 14 (**a**–**c**) or 21 days (**d**–**f**) of daily continuous applications of PBM. Hematoxylin and eosin, x 40

Results

Effects of PBM on mechanical sensitivity of rats with persistent orofacial pain

CFA induced a significant decrease of the mechanical sensitivity of rats detected 7 days after its injection and maintained throughout 21 days of evaluation (CFA: day 0, 98.96 ± 3.25; day 7 45.96 ± 2.84, $n = 11$) (Fig. 1). A single application of PBM therapy was able to reverse the observed nociception up to 6 h of evaluation (CFA+PBM: day 7 51.56 ± 3.51; 1 h 57.21 ± 4.31; 3 h 59.76 ± 3.19; 6 h 60.59 ± 4.0, $n = 11$; $p = 0.0087$) when compared to the group of rats that received SHAM irradiation (CFA+PBM Off: day 7 44.80 ± 3.18; 1 h 47.61 ± 3.88; 3 h 47.34 ± 3.02; 6 h 47.53 ± 3.42, $n = 11$), decreasing at 24 h of evaluation (Fig. 1a). Continuous treatment with PBM maintained the antinociceptive effect evaluated both after 7 (CFA+PBM: 51.56 ± 3.51, CFA+PBM Off: 44.80 ± 3.19, $n = 11$; $p = 0.00029$) or 14 days (CFA+PBM: 75.07 ± 3.59, CFA+PBM Off: 54.05 ± 3.2, $n = 11$; $p = 0.0009$) of treatment (Fig. 1b). No changes on mechanical sensitivity were observed for the control group of rats treated with saline (Fig. 1b). All data are represented as mean ± SEM of the intensity threshold, in grams, required for an animal's head withdrawal reflex force.

Effects of PBM on muscle regeneration in the masseter of rats with persistent orofacial pain

Morphological analysis of the masseter muscle demonstrated that PBM *reverses* the intense inflammatory reaction induced by CFA. Moreover, PBM inhibited cellular degeneration and induced regeneration of muscular cells demonstrated by the presence of muscular fibers with centrally located nuclei, denoting that they are immature, newly formed muscle cells thus suggesting that PBM not only inhibited CFA-induced inflammatory reaction but also induced tissue repair (Fig. 2).

Effects of PBM on fractalkine expression in the trigeminal ganglia of rats

Besides a slightly decrease on Iba-IR in the CFA+PBM On group, no significant changes on microglial expression were observed in the trigeminal ganglia of rats evaluated by

immunohistochemistry (Fig. 3a). On the other hand, PBM significantly decreased FKT-IR (CFA+PBM On: 823.7 ± 30.25; $p = 0.0007$) when compared to the CFA (1175 ± 42.8) or CFA+PBM Off (1202 ± 33.91) groups (Fig. 3b).

Discussion

In this study, we examined the effects of PBM in an experimental model of temporomandibular disorder induced by complete Freund adjuvant (CFA) injection in the masseter of rats as well as part of the mechanisms involved.

CFA elicits an intense inflammatory response, followed by an intense mechanical hyperalgesia that persists for hours or days [33]. Our results demonstrate that single intramuscular application of CFA-induced hyperalgesia in animals for at least 21 days of evaluation. These data are in agreement with those of previous studies that showed presence of mechanical allodynia, hyperalgesia, and extensive infiltration of inflammatory cells in different models of orofacial pain and inflammation in rats after CFA application [6, 34, 35].

Literature demonstrates that PBM reduces pain in patients with myofascial pain syndrome and chronic muscular TMD, inducing and improvement of orofacial myofunctional conditions, mouth opening, and masticatory performance [36–40]. Our results demonstrated that a single application of PBM (InGaAlP, 660 nm, 30 mW, 1.6 J/cm^2, 0.2 cm^2, 15 s of continuous irradiation) after 7 days of CFA injection was able to reverse the observed hyperalgesia for up to 24 h. The 660-nm wavelength chosen herein is described as effective in inducing antinociception and wound healing in experimental models [41]. It is also demonstrated that this wavelength is able to modulate cell viability, proliferation, and gene expression of various cell adhesion molecules contributing to the increased wound healing seen in clinical practice [42, 43]. Moreover, consecutive daily sessions maintained the observed antinopciception for up to 14 days of evaluation, thus reinforcing that more applications are necessary to maintain the observed analgesia and confirming the beneficial effect of this therapy as an adjuvant of the treatment of TMD. Moreover, PBM significantly decreased inflammatory response and induced tissue healing in the masseter of rats demonstrated by the decrease of inflammatory infiltrate and the presence of newly formed, centralized nuclei-immature muscular fibers.

To further analyze the mechanism by which PBM-induced antinociception, we evaluated the involvement of microglia and fractalkine in central levels. Data presented herein demonstrated a slight but not significant decrease of microglial expression in the trigeminal ganglia of CFA rats. On the other hand, a significant decrease of fractalkine (FKN) expression was observed. This data corroborates with data demonstrating the involvement of FKN in different models of experimental neuropathic pain, reinforcing the role of PBM in the central

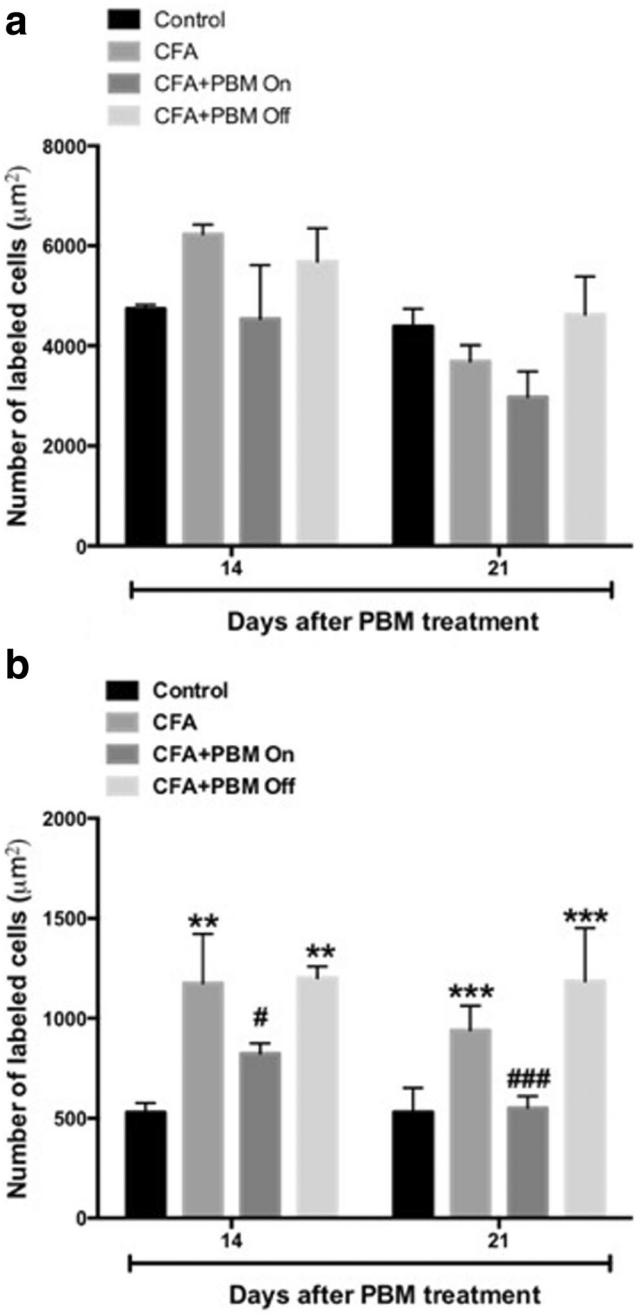

Fig. 3 Effect of PBM on microglia or fractalkine expression in the trigeminal ganglia of TMD rats. **a** Microglia or **b** fractalkine expression in the trigeminal ganglion of rats injected with CFA, CFA+PBM On, CFA+PBM Off, or saline (control) after 14 or 21 days of consecutive PMB applications. Data correspond to the mean ± S.E.M. of three rats per group. $^{**}p < 0.01$, $^{***}p < 0.001$, when comparing CFA or CFA+PBM Off to the control group; $\#p < 0.05$, $\#\#\#p < 0.001$ when comparing CFA+PBM On to the CFA group (one-way ANOVA)

inhibition of the inflammatory response [44]. One hypothesis is that FKN expression in neurons activates microglial cells to induce inflammation and hyperalgesia, indicating that the facilitatory mechanisms in the nociceptive pathway may involve the activation of CX3CR1 receptors in microglia, by the

fractalkine [24, 29, 45–47]. The exact mechanisms by which PBM inhibits inflammatory hyperalgesia in experimental TMD are under investigation. Taken together, data presented herein provided new evidence of the use of PBM therapy as a therapeutical tool to treat TMD.

Conclusion

PBM induces true antinociception, through the central inhibition of fractalkine, in rats submitted to an experimental model of TMD. These data have direct clinical application for patients with TMD. The exact mechanisms by which PBM reverses pain in TMD still need to be elucidated and are under investigation in our laboratory.

Acknowledgements CSD thanks the National Council for Scientific and Technological Development (CNPq, Brazil) for the productivity fellowship. ACF thanks FAPESP for the PhD grant (FAPESP 2012/03865-0). ETS and EFT thank for CNPq grants.

Funding This work was supported by FAPESP (grant no. 2015/17136-8). The authors declare no conflicts of interest.

Compliance with ethical standards Throughout the experiments, animals were managed using the principles and guidelines for the care of laboratory animals in studies involving pain and were approved by the Ethics Committee on the Use of Animals at University of São Paulo (CEUA, protocol no. 020/2014).

Conflict of interest The authors declare that they have no conflicts of interest.

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