Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Photobiomodulation Modulates Peripheral and Central Expression of Inflammation-Related Genes Following Carrageenan-Induced Inflammation in Rats

Carlos Alberto-Silva
Universidade Federal do ABC
Giulia Nicolle Jácome Cartaxo
Universidade do Vale do Paraíba
Regiane dos Santos Feliciano
Universidade Nove de Julho
Bruna Calixto de Jesus
Universidade Nove de Julho
José Antônio Silva-Junior3
Universidade Nove de Julho
Maricilia Silva Costa
mscosta@univap.br

Universidade do Vale do Paraíba

Research Article

Keywords: Photobiomodulation, Peripheral inflammation, Kinin receptors, Interleukin-6, Interleukin-10, Prostacyclin receptor

Posted Date: September 28th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10910451/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Purpose

Peripheral inflammation can induce molecular changes in central nervous system through immune–brain communication. This study investigated whether photobiomodulation (PBM) modulates the temporal mRNA expression of pro- and anti-inflammatory cytokines and receptors involved in prostacyclin and kinin signaling in peripheral and central tissues following carrageenan-induced inflammation in rats.

Methods

Male Wistar rats received subplantar carrageenan injections (1 mg/paw) and were treated or not with PBM (660 nm) 1 h after carrageenan administration. Animals were euthanized at 1, 3, or 6 h, and mRNA expression of IL-6, IL-10, prostacyclin receptor (IP), and kinin B1 and B2 receptors was quantified by qRT-PCR in subplantar and brain tissues.

Results

IL-6 and IP receptor mRNA expression increased predominantly at 6 h and was reduced by PBM at this time point in both subplantar and brain tissues. In the paw, B1 receptor expression peaked at 3 h and was reduced by PBM, whereas B2 receptor expression showed its greatest increase at 6 h. In the brain, PBM reduced B1 and B2 receptor expression at 6 h. IL-10 expression increased in the paw, remaining elevated in PBM-treated animals. In the brain, IL-10 expression increased at 3 h and decreased at 6 h after carrageenan administration, whereas PBM maintained elevated IL-10 expression at 6 h.

Conclusion

Carrageenan-induced peripheral inflammation was accompanied by time-dependent changes in inflammation- and nociception-related gene expression in brain tissue. Localized PBM modulated these peripheral and central transcriptional responses by reducing IL-6, IP, and kinin receptor expression at specific time points while maintaining elevated IL-10 expression. These findings extend previous observations by demonstrating coordinated modulation of cytokine, prostacyclin, and kinin signaling-related genes following localized PBM.

1. Introduction

The bidirectional communication between the peripheral immune system and the central nervous system (CNS) is increasingly recognized as an important determinant of neurological function and health. Accumulating evidence indicates that inflammation initiated in peripheral tissues can influence

brain function and trigger central inflammatory responses, even when the initial insult is localized. Such peripheral–central interactions have been associated with alterations in higher-order cognitive functions and other neurological outcomes [1]. Although acute conditions such as systemic infections or traumatic injuries generally elicit transient inflammatory responses [2], peripheral immune activation can also influence CNS function and contribute to neuroinflammatory processes. Neuroinflammation represents an important component of peripheral–brain communication and may contribute to neurological dysfunction following peripheral inflammatory insults [3]. Peripheral inflammatory challenges have also been shown to induce changes in glial activity, including the activation of microglia and astrocytes, which transition into reactive states following peripheral immune stimulation [4]. A well-established experimental approach for investigating peripheral inflammatory responses and their consequences for central signaling is the carrageenan-induced paw inflammation model, which reliably produces acute inflammation and hyperalgesia and has been extensively used to investigate the molecular mechanisms underlying inflammatory responses and pain [5].

Subplantar injection of carrageenan induces a well-characterized biphasic inflammatory response involving the sequential release and action of several inflammatory mediators. The early phase is associated predominantly with the release of vasoactive mediators, including histamine and bradykinin, whereas the later phase involves increased production of prostanoids and pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) in the inflamed tissue [6–8]. The kinin and prostanoid systems play important roles in inflammatory pain, with bradykinin signaling involving B2 receptors and, particularly under inflammatory conditions, inducible B1 receptors [9]. Prostacyclin signaling through the IP receptor also contributes to inflammatory nociception and pain sensitization [10]. Importantly, the inflammatory consequences of carrageenan-induced peripheral injury are not restricted to the site of injection. Experimental studies have demonstrated that this localized inflammatory challenge can induce changes in inflammatory mediators and related signaling pathways within the CNS, indicating that peripheral inflammation can engage mechanisms of peripheral–brain communication [11–13].

In this context, photobiomodulation (PBM) has emerged as a promising non-invasive approach for modulating inflammatory responses. Increasing evidence indicates that PBM can influence multiple cellular and molecular pathways involved in inflammation, including the regulation of cytokine production and signaling associated with inflammatory and pain responses [14–16]. Importantly, our previous study demonstrated that 660 nm PBM reduces IL-1β, mPGES-1, and mPGES-2 mRNA expression in both inflamed paw and brain tissues, whereas EP receptor expression was not significantly affected [17]. Earlier findings from this experimental model also demonstrated reduced COX-2 mRNA expression following PBM [18]. These findings provided evidence that localized PBM can modulate inflammatory signaling beyond the site of irradiation, including within the CNS. Building on these findings, the present study investigated whether localized PBM can modulate additional components of the peripheral and central inflammatory response following carrageenan-induced peripheral inflammation. Specifically, we evaluated the temporal expression of IL-6 and the anti-inflammatory cytokine IL-10, together with the prostacyclin (IP) receptor and kinin B1 and B2 receptors, in both paw

and brain tissues. Together, these targets provide a complementary view of the inflammatory response by surrounding pro- and anti-inflammatory cytokine signaling combined with receptor systems involved in kinin- and prostanoid-mediated inflammatory processes. By comparing their expression profiles across peripheral and central tissues and different stages of inflammation, we investigated whether PBM produces coordinated molecular effects beyond the previously characterized regulation of IL-1β, COX-2, mPGES-1, and mPGES-2 [17]. We hypothesized that localized 660 nm PBM would modulate inflammation-associated gene expression by reducing selected pro-inflammatory and nociception-related mediators while preserving the expression of the regulatory cytokine IL-10 in peripheral and brain tissues.

2. Material and Methods

2.1. Chemicals and animals

Male Wistar rats aged 5–7 weeks and weighing 150–200 g were obtained from the Central Animal House of the _____. All experimental procedures were approved by the _____. Animals were housed six per cage at 25°C and 50% ± 15% relative humidity under a 12-h light/dark cycle with constant ventilation and had *ad libitum* access to standardized laboratory chow and water.

2.2. Peripheral inflammation model and experimental design

Peripheral inflammation was induced by subplantar administration of carrageenan, as previously described [17]. Thirty-six male Wistar rats were randomly allocated to six experimental groups (n = 6 per group). Under anesthesia with 1% halothane (Sigma Chemical Co., St. Louis, MO, USA), animals received a subplantar injection of approximately 100 µL of carrageenan solution (1 mg/paw; Sigma Chemical Co., St. Louis, MO, USA) diluted in 0.90% NaCl into the left hind paw using a 27-gauge needle.

The experimental groups were defined according to carrageenan administration, PBM treatment, and time of euthanasia: Control, animals receiving 0.90% NaCl and euthanized 6 h after injection; Carr-1, Carr-3, and Carr-6, animals receiving carrageenan and euthanized 1, 3, or 6 h after injection, respectively; Carr + PBM-1, animals receiving carrageenan, treated with PBM 1 h after carrageenan administration, and euthanized 3 h after injection; and Carr + PBM-6, animals receiving carrageenan, treated with PBM 1 h after carrageenan administration, and euthanized 6 h after injection. The overall experimental design and timeline are summarized in the Fig. 1. Animals were euthanized by CO_2 asphyxiation. Subplantar tissue from the injected paw and brain tissue were rapidly collected on a cold plate, immediately frozen in liquid nitrogen, and stored at − 80°C until RNA extraction.

2.3. Photobiomodulation parameters

Photobiomodulation was performed using a diode laser emitting at 660 nm with an output power of 30 mW (Laser Unit, Kondortech, São Carlos, SP, Brazil). The laser beam covered an area of 0.785 cm² and

was applied to the plantar surface of the inflamed paw at a distance of 1.2 cm. The irradiation parameters corresponded to an energy density of 7.5 J/cm² and a total irradiation time of 196 s per application, as previously described [17].

2.4. Quantitative real-time PCR (qRT-PCR)

Tissue samples (0.2–0.5 g) were homogenized in TRIzol® Reagent for total RNA extraction. Complementary DNA (cDNA) was synthesized by reverse transcription using the following conditions: 25°C for 10 min, 37°C for 120 min, and 85°C for 5 min. Quantitative real-time PCR (qRT-PCR) was performed using TaqMan™ Universal Fast Master Mix (2×), with 1 µL of cDNA in a final reaction volume of 10 µL per well. Amplification was performed using an ABI Prism 7500 Fast Real-Time PCR System (Applied Biosystems, Carlsbad, CA, USA), with an initial step at 95°C for 20 s followed by 40 amplification cycles. Gene expression levels were normalized to 18S rRNA, which was used as the endogenous reference gene. Data were processed using SDS 1.4 software (Applied Biosystems, Carlsbad, CA, USA). The relative expression of IL-6, IL-10, the prostacyclin (IP) receptor, and kinin B1 and B2 receptors was determined in subplantar and brain tissues using the 2^−ΔΔCt method. ΔCt values were calculated by subtracting the mean Ct value of the target gene from the mean Ct value of 18S rRNA, as previously described [17]. Samples were analysed in duplicate.

2.5. Statistical analysis

Data are presented as mean ± standard deviation (SD), with n = 6 animals per experimental group. Statistical significance was assessed using one-way analysis of variance (ANOVA), followed by the Tukey–Kramer post-hoc test for multiple comparisons. Differences were considered statistically significant at $P < 0.05$. Statistical analyses were performed using GraphPad Prism 7.0 (GraphPad Software, La Jolla, CA, USA).

3. Results

3.1. PBM attenuates IP receptor and IL-6 mRNA expression in subplantar and brain tissues

In the paw, carrageenan administration induced an increase in IP receptor mRNA expression, with the highest level observed at 6 h post-injection (Fig. 2a). At this time point, PBM significantly reduced IP receptor expression compared with the corresponding carrageenan group. Although, IP receptor mRNA expression showed a different temporal pattern in the brain, with increased expression at 1 h, lower levels at 3 h, and a subsequent increase at 6 h. PBM significantly reduced IP receptor expression at 6 h compared with Carr-6 (Fig. 2b). A similar late response was observed for IL-6. In the paw, IL-6 mRNA expression increased following carrageenan administration, with higher levels at 3 and 6 h and the highest expression at 6 h. PBM significantly reduced IL-6 expression at 6 h compared with Carr-6 (Fig. 2c). In the brain, IL-6 expression was markedly increased at 6 h after carrageenan administration and was significantly reduced by PBM at the same time point (Fig. 2d).

3.2. PBM maintains elevated IL-10 mRNA expression following carrageenan-induced inflammation

IL-10 mRNA expression in the paw increased following carrageenan administration, with higher levels observed at 3 and 6 h (Fig. 3a). In PBM-treated animals, IL-10 expression remained elevated at both time points. However, a different temporal profile was observed in the brain, with IL-10 expression increasing at 3 h and subsequently decreasing at 6 h after carrageenan administration. In animals treated with PBM, IL-10 expression remained elevated at 6 h (Fig. 3b).

3.3. PBM differentially modulates kinin B1 and B2 receptor mRNA expression in subplantar and brain tissues

Kinin B1 receptor mRNA expression increased following carrageenan administration, reaching its highest level at 3 h, in the paw (Fig. 4a). At this time point, PBM significantly reduced B1 receptor expression compared with Carr-3. In the brain, B1 receptor expression showed a biphasic pattern, with increased expression at 1 h, lower levels at 3 h, and a subsequent increase at 6 h. PBM significantly reduced B1 receptor expression at 6 h compared with Carr-6 (Fig. 4b). Kinin B2 receptor mRNA expression in the paw also increased following carrageenan administration, reaching its highest level at 6 h (Fig. 4c). In PBM-treated animals, B2 receptor expression at 3 and 6 h remained below the marked increase observed in the Carr-6 group. In the brain, B2 receptor expression increased at 1 h, decreased at 3 h, and reached its highest level at 6 h. PBM significantly reduced B2 receptor expression at 6 h compared with Carr-6 (Fig. 4d).

4. Discussion

The principal finding of this study is that localized PBM produced coordinated and time-dependent changes in inflammation- and nociception-related gene expression in both the inflamed paw and total brain tissue. Specifically, PBM attenuated IL-6, IP, and kinin B1 and B2 receptor mRNA expression at specific time points while maintaining elevated expression of the regulatory cytokine IL-10. These results indicate that the molecular response associated with localized PBM is not restricted to the irradiated tissue and involves multiple components of the peripheral and central inflammatory response. An integrated overview of the peripheral and central transcriptional responses observed at the final experimental time point is presented in Fig. 5. These findings are consistent with evidence that peripheral inflammatory stimuli can be accompanied by molecular changes in the CNS [1, 3].

Peripheral inflammatory signals can reach the brain through neural and humoral pathways, providing a biological basis for the central responses observed following a peripheral inflammatory challenge [19]. Previous studies using carrageenan-induced peripheral inflammation have also demonstrated changes in inflammatory mediators within the CNS, further supporting the communication between peripheral inflammatory events and central molecular responses [11, 12, 17]. The present findings extend these

previous observations by demonstrating the involvement of pro- and anti-inflammatory cytokines and components of the kinin–kallikrein system in the molecular response associated with localized PBM. These findings are consistent with the immunomodulatory effects of PBM reported in different experimental models [14–16, 20].

The kinin–kallikrein system was markedly modulated by PBM, particularly through changes in B1 and B2 receptor expression. These receptors play important roles in inflammatory and nociceptive responses, and their expression may vary according to the inflammatory condition and its temporal evolution [9]. In the paw, kinin receptor expression showed a time-dependent response to carrageenan, with B1 receptor mRNA reaching its highest level at 3 h, whereas B2 receptor mRNA showed its greatest increase at 6 h. PBM reduced B1 receptor expression at 3 h, while B2 receptor expression at 3 and 6 h remained below the marked increase observed in the Carr-6 group. These findings indicate that PBM modulates kinin receptor expression during the progression of the peripheral inflammatory response. In agreement with these results, de Oliveira et al. [21], analyzing inflammatory and pain mediators after papain-induced osteoarthritis in rats, observed attenuated mRNA and protein levels of kinin B1 and B2 receptors following PBM. Changes in kinin receptor expression were also observed in the brain, where PBM reduced B1 and B2 receptor mRNA expression at 6 h. This finding suggests that the effects associated with localized PBM are accompanied by molecular changes beyond the irradiated tissue, including the modulation of inflammation-associated pathways in the CNS. Manchini et al. [22] also observed reduced B1 receptor expression after PBM in inflamed subplantar muscle, but increased B2 receptor mRNA expression 72 h after myocardial infarction. Such differences may be related to the experimental model, tissue environment, and time after injury. In addition, previous evidence demonstrates functional cross-talk between B1 and B2 receptors, including B2-mediated regulation of B1 receptor signaling and desensitization, indicating that the activity of these receptors may not occur independently under inflammatory conditions [23]. Thus, the different temporal profiles observed for B1 and B2 receptor expression in the present study may reflect the dynamic regulation of the kinin system during the inflammatory response.

The central molecular response observed in this study was also evident for IL-6 and the IP receptor. IL-6 is a pleiotropic cytokine involved in the regulation and progression of inflammatory responses [24] and has also been proposed as an important mediator of inflammatory communication between peripheral tissues and the CNS. In a carrageenan-induced inflammatory model, Oka et al. [12] demonstrated that circulating IL-6 may act as a messenger of inflammatory information from the peripheral inflammatory site to the CNS. In the present study, IL-6 mRNA expression increased markedly at 6 h in both the paw and brain, whereas PBM significantly reduced its expression at this time point. This parallel response further supports the close relationship between peripheral inflammatory events and central molecular changes and indicates that PBM can modulate IL-6 expression at both levels. A similar effect was observed for the IP receptor. Prostacyclin signaling through the IP receptor plays an important role in inflammatory pain and contributes to nociceptor sensitization [10]. In the present study, IP receptor mRNA expression increased at 6 h after carrageenan administration and was significantly reduced by PBM in both paw and brain tissues. Therefore, modulation of IP receptor expression may contribute to

the effects of PBM on inflammatory and nociceptive signaling. These findings are supported by Chagas et al. [25], who demonstrated increased IP receptor mRNA expression in both subplantar and brain tissues 6 h after carrageenan-induced peripheral inflammation and a significant reduction following 660 nm irradiation. Together with the present findings, these results reinforce the involvement of prostanoid signaling in the molecular response to PBM during carrageenan-induced inflammation.

Another relevant finding was the modulation of IL-10, an anti-inflammatory cytokine involved in the control and resolution of inflammatory responses. Previous studies have demonstrated that photobiomodulation can modulate IL-10 production in different inflammatory conditions [26–28]. In the paw, IL-10 mRNA expression increased after carrageenan administration and remained elevated in PBM-treated animals at 3 and 6 h. In the brain, IL-10 expression increased at 3 h following carrageenan administration and subsequently decreased at 6 h, whereas expression remained elevated at 6 h in PBM-treated animals. In contrast to the reduction observed for IL-6, IP, and kinin receptors at specific time points, the maintenance of IL-10 expression suggests that PBM does not act exclusively by reducing inflammation-associated mediators but may also favor regulatory mechanisms involved in the control of the inflammatory response.

Taken together, the temporal changes observed in the paw and brain demonstrate that carrageenan-induced peripheral inflammation is accompanied by rapid changes in the expression of inflammatory and nociceptive mediators in the CNS. Local PBM modulated this response in both tissues, reducing IL-6, IP receptor, and kinin receptor mRNA expression at specific time points while maintaining elevated IL-10 expression. These findings extend previous observations from this experimental model by showing that the molecular effects associated with local PBM involve not only prostanoid and cytokine pathways but also components of the kinin–kallikrein system. Although the mechanisms linking local PBM to changes in brain gene expression remain to be established, the present results support a multi-target immunomodulatory effect of PBM and demonstrate that its molecular effects are not restricted to the irradiated tissue.

Declarations

Author Contribution

Author contributions1. Carlos Alberto-Silva - Writing-original draft preparation; Formal analysis and investigation; Writing-review and editing2. Giulia Nicolle Jácome Cartaxo - Formal analysis and investigation3. Regiane dos Santos Feliciano - Formal analysis and investigation 4. Bruna Calixto de Jesus - Formal analysis and investigation5. José Antônio Silva-Junior - Writing-original draft preparation; Methodology; Conceptualization; Formal analysis and investigation; Supervision6. Maricilia Silva Costa - Writing-original draft preparation; Writing-review and editing; Formal analysis and investigation; Funding acquisition; Conceptualization; Resources; Supervision

Acknowledgement

AcknowledgementsThis work was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP). This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001.

References

1. Geloso MC, Zupo L, Corvino V (2024) Crosstalk between peripheral inflammation and brain: Focus on the responses of microglia and astrocytes to peripheral challenge. Neurochem Int 180:105872. https://doi.org/10.1016/j.neuint.2024.105872
2. Stiel L, Gaudet A, Thietart S, Vallet H, Bastard P, Voiriot G, Oualha M, Sarton B, Kallel H, Brechot N, Kreitmann L, Benghanem S, Joffre J, Jouan Y (2024) Innate immune response in acute critical illness: a narrative review. Ann Intensive Care 14(1):137. https://doi.org/10.1186/s13613-024-01355-6
3. Sun Y, Koyama Y, Shimada S (2022) Inflammation From Peripheral Organs to the Brain: How Does Systemic Inflammation Cause Neuroinflammation? Front Aging Neurosci 14:903455. https://doi.org/10.3389/fnagi.2022.903455
4. Hoogland IC, Houbolt C, van Westerloo DJ, van Gool WA, van de Beek D (2015) Systemic inflammation and microglial activation: systematic review of animal experiments. J Neuroinflammation 12:114. https://doi.org/10.1186/s12974-015-0332-6
5. Patil KR, Mahajan UB, Unger BS, Goyal SN, Belemkar S, Surana SJ, Ojha S, Patil CR (2019) Animal Models of Inflammation for Screening of Anti-inflammatory Drugs: Implications for the Discovery and Development of Phytopharmaceuticals. Int J Mol Sci 20(18):4367. https://doi.org/10.3390/ijms20184367
6. Burch RM, DeHaas C (1990) A bradykinin antagonist inhibits carrageenan edema in rats. Naunyn Schmiedebergs Arch Pharmacol 342(2):189–193. https://doi.org/10.1007/BF00166963
7. Kirchhoff C, Jung S, Reeh PW, Handwerker HO (1990) Carrageenan inflammation increases bradykinin sensitivity of rat cutaneous nociceptors. Neurosci Lett 111(1–2):206–210. https://doi.org/10.1016/0304-3940(90)90369-k
8. Posadas I, Bucci M, Roviezzo F, Rossi A, Parente L, Sautebin L, Cirino G (2004) Carrageenan-induced mouse paw oedema is biphasic, age-weight dependent and displays differential nitric oxide cyclooxygenase-2 expression. Br J Pharmacol 142(2):331–338. https://doi.org/10.1038/sj.bjp.0705650
9. Calixto JB, Cabrini DA, Ferreira J, Campos MM (2000) Kinins in pain and inflammation. Pain 87(1):1–5. https://doi.org/10.1016/S0304-3959(00)00335-3
10. Bley KR, Hunter JC, Eglen RM, Smith JA (1998) The role of IP prostanoid receptors in inflammatory pain. Trends Pharmacol Sci 19(4):141–147. https://doi.org/10.1016/s0165-6147(98)01185-7

11. Guay J, Bateman K, Gordon R, Mancini J, Riendeau D (2004) Carrageenan-induced paw edema in rat elicits a predominant prostaglandin E2 (PGE2) response in the central nervous system associated with the induction of microsomal PGE2 synthase-1. J Biol Chem 279(23):24866–24872. https://doi.org/10.1074/jbc.M403106200
12. Oka Y, Ibuki T, Matsumura K, Namba M, Yamazaki Y, Poole S, Tanaka Y, Kobayashi S (2007) Interleukin-6 is a candidate molecule that transmits inflammatory information to the CNS. Neuroscience 145(2):530–538. https://doi.org/10.1016/j.neuroscience.2006.10.055
13. Kono K, Okada A, Ishikawa A, Aiba T (2013) Effect of carrageenan-induced acute peripheral inflammation on the electrolyte disposition to cerebrospinal fluid in rats. Biol Pharm Bull 36(11):1829–1834. https://doi.org/10.1248/bpb.b13-00531
14. Albertini R, Villaverde AB, Aimbire F, Bjordal J, Brugnera A, Mittmann J, Silva JA, Costa M (2008) Cytokine mRNA expression is decreased in the subplantar muscle of rat paw subjected to carrageenan-induced inflammation after low-level laser therapy. Photomed Laser Surg 26(1):19–24. https://doi.org/10.1089/pho.2007.2119
15. Hamblin MR (2018) Mechanisms and Mitochondrial Redox Signaling in Photobiomodulation. Photochem Photobiol 94(2):199–212. https://doi.org/10.1111/php.12864
16. Mattoso-Câmara AR, Papini JZB, Teixeira MA, Fujii DN, Tofoli GR, Garcez AS (2026) Targeting pain and inflammation: A comparative study of photobiomodulation with 532 and 660 nm lasers in rats. Photochem Photobiol 102(2):520–528. https://doi.org/10.1111/php.70013
17. Alberto-Silva C, de Souza Calvi G, Dos Santos Feliciano R, Silva-Junior JA, Costa MS (2025) Anti-inflammatory effect of photobiomodulation in the brain following local peripheral carrageenan-induced inflammation. Lasers Med Sci 40(1):272. https://doi.org/10.1007/s10103-024-04205-w
18. Prianti AC Jr, Silva JA Jr, Dos Santos RF, Rosseti IB, Costa MS (2014) Low-level laser therapy (LLLT) reduces the COX-2 mRNA expression in both subplantar and total brain tissues in the model of peripheral inflammation induced by administration of carrageenan. Lasers Med Sci 29(4):1397–1403. https://doi.org/10.1007/s10103-014-1543-2
19. Dantzer R, Konsman JP, Bluthé RM, Kelley KW (2000) Neural and humoral pathways of communication from the immune system to the brain: parallel or convergent? Auton Neurosci 85(1–3):60–65. https://doi.org/10.1016/S1566-0702(00)00220-4
20. Nasuk GR, de Matos LP, Atum ALB, de Jesus BC, Batista JGC, da Silva GA, Martins AH, Trivelin MLA, Duran CCG, de Oliveira APL, Prates RA, Marcos RL, Zamuner SR, Baltatu OC, Silva JA Jr (2025) Photobiomodulation Therapy Reduces Oxidative Stress and Inflammation to Alleviate the Cardiotoxic Effects of Doxorubicin in Human Stem Cell-Derived Ventricular Cardiomyocytes. Biomedicines 13(7):1781. https://doi.org/10.3390/biomedicines13071781
21. de Oliveira VL, Silva JA Jr, Serra AJ, Pallotta RC, da Silva EA, de Farias Marques AC, Feliciano RD, Marcos RL, Leal-Junior EC, de Carvalho PT (2017) Photobiomodulation therapy in the modulation of inflammatory mediators and bradykinin receptors in an experimental model of acute osteoarthritis. Lasers Med Sci 32(1):87–94. https://doi.org/10.1007/s10103-016-2089-2

22. Manchini MT, Serra AJ, Feliciano Rdos S, Santana ET, Antônio EL, de Tarso P, Montemor J, Crajoinas RO, Girardi AC, Tucci PJ, Silva JA Jr (2014) Amelioration of cardiac function and activation of anti-inflammatory vasoactive peptides expression in the rat myocardium by low level laser therapy. PLoS One 9(7):e101270. https://doi.org/10.1371/journal.pone.0101270
23. Zhang X, Brovkovych V, Zhang Y, Tan F, Skidgel RA (2015) Downregulation of kinin B1 receptor function by B2 receptor heterodimerization and signaling. Cell Signal 27(1):90–103. https://doi.org/10.1016/j.cellsig.2014.09.019
24. Lacina L, Kolář M, Pfeiferová L, Gál P, Smetana K Jr (2024) Wound healing: insights into autoimmunity, ageing, and cancer ecosystems through inflammation and IL-6 modulation. Front Immunol 15:1403570. https://doi.org/10.3389/fimmu.2024.1403570
25. Chagas LR, Silva JA Jr, de Almeida Pires J, Costa MS (2015) Expression of mPGES-1 and IP mRNA is reduced by LLLT in both subplantar and brain tissues in the model of peripheral inflammation induced by carrageenan. Lasers Med Sci 30(1):83–88. https://doi.org/10.1007/s10103-014-1622-4
26. Martins DF, Turnes BL, Cidral-Filho FJ, Bobinski F, Rosas RF, Danielski LG, Petronilho F, Santos AR (2016) Light-emitting diode therapy reduces persistent inflammatory pain: Role of interleukin 10 and antioxidant enzymes. Neuroscience 324:485–495. https://doi.org/10.1016/j.neuroscience.2016.03.035
27. Tolentino M, Cho CC, Lyons JÁ (2022) Photobiomodulation Modulates Interleukin-10 and Interferon Gamma Production by Mononuclear Cells from Healthy Donors and Persons with Multiple Sclerosis. Photobiomodul Photomed Laser Surg 40(4):234–244. https://doi.org/10.1089/photob.2021.0169
28. de Brito AA, Gonçalves Santos T, Herculano KZ, Estefano-Alves C, de Alvarenga Nascimento CR, Rigonato-Oliveira NC, Chavantes MC, Aimbire F, da Palma RK, de Ligeiro AP (2022) Photobiomodulation Therapy Restores IL-10 Secretion in a Murine Model of Chronic Asthma: Relevance to the Population of $CD4^{+}CD25^{+}Foxp3^{+}$ Cells in Lung. Front Immunol 12:789426. https://doi.org/10.3389/fimmu.2021.789426

Figures

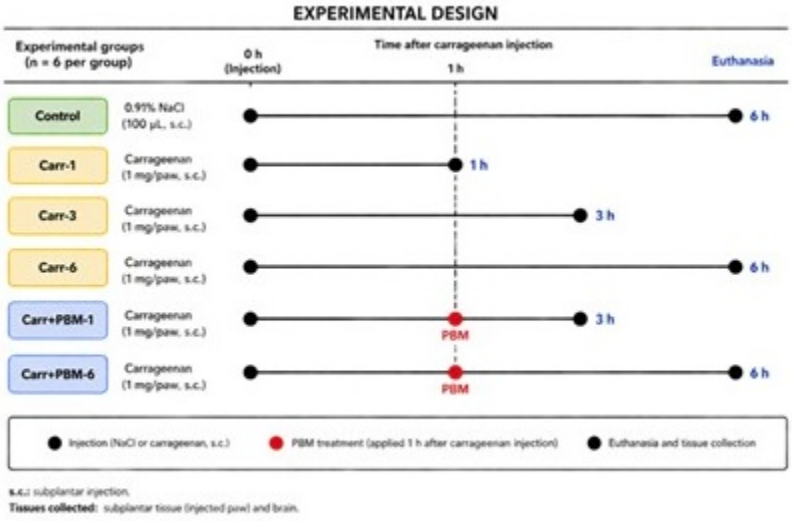


Figure 1

Experimental design and timeline. Male Wistar rats were allocated into six groups (n = 6/group) according to carrageenan administration, PBM treatment, and euthanasia time (1, 3, or 6 h). The control group received a subplantar injection of saline and was euthanized at 6 h. Carrageenan-treated animals received 1 mg/paw and were euthanized at 1, 3, or 6 h. PBM (660 nm) was applied to the inflamed paw 1 h after carrageenan injection, and PBM-treated animals were euthanized at 3 or 6 h. Subplantar and total brain tissues were collected immediately after euthanasia. PBM, photobiomodulation; Carr, carrageenan

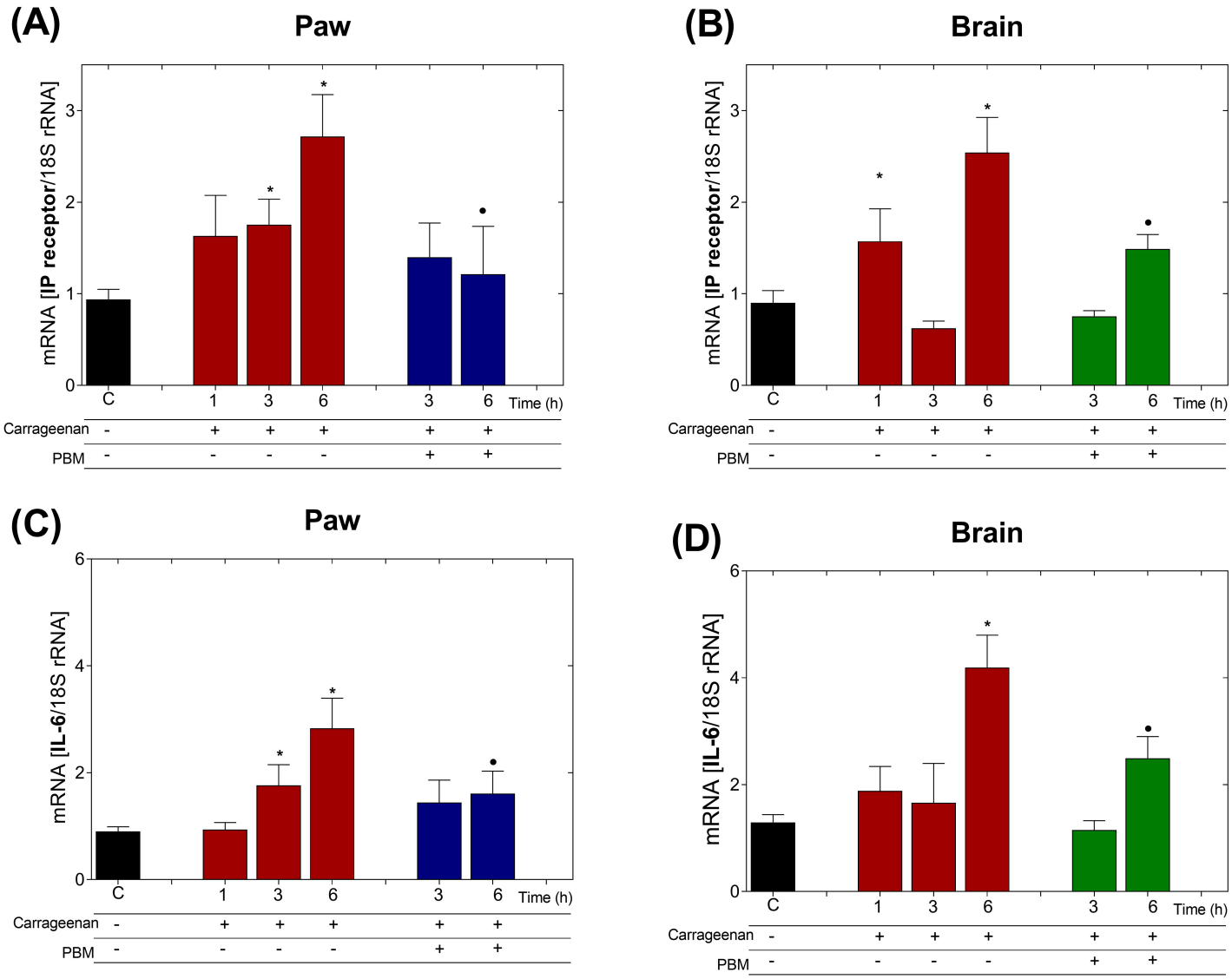


Figure 2

PBM attenuates IP receptor and IL-6 mRNA expression following carrageenan-induced peripheral inflammation. IP receptor mRNA expression was evaluated in subplantar tissue (A) and total brain tissue (B), whereas IL-6 mRNA expression was evaluated in subplantar tissue (C) and total brain tissue (D). Gene expression was quantified by qRT-PCR, normalized to 18S rRNA expression, and presented as relative mRNA expression. Data are presented as mean ± SD of six animals per experimental group (n = 6) and were analyzed by one-way ANOVA followed by the Tukey–Kramer post hoc test. Different symbols indicate significant differences ($p < 0.05$): *, compared with the saline-treated control group; ●, compared with the carrageenan group at 6 h. C, saline-treated control; PBM, photobiomodulation

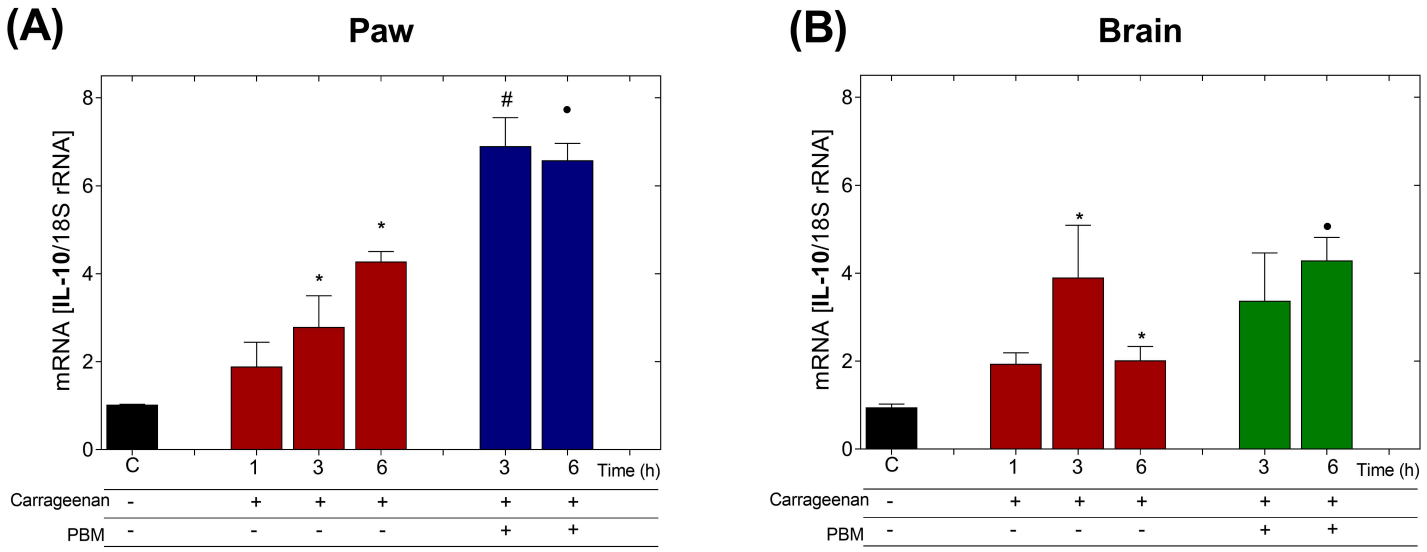


Figure 3

PBM preserves IL-10 mRNA expression during carrageenan-induced peripheral inflammation. IL-10 expression increased in subplantar tissue at 3 and 6 h and remained elevated in PBM-treated animals (A). In total brain tissue, IL-10 expression showed a transient increase at 3 h followed by a decrease at 6 h, whereas PBM maintained elevated expression at the later time point (B). IL-10 mRNA was quantified by qRT-PCR and normalized to 18S rRNA. Results are expressed as mean ± SD for six animals per group. Differences among experimental groups were assessed by one-way ANOVA followed by the Tukey–Kramer post hoc test. Different symbols indicate significant differences ($p < 0.05$): *, versus the saline-treated control group; #, versus the carrageenan group at 3 h; and ●, versus the carrageenan group at 6 h. C, saline-treated control; PBM, photobiomodulation

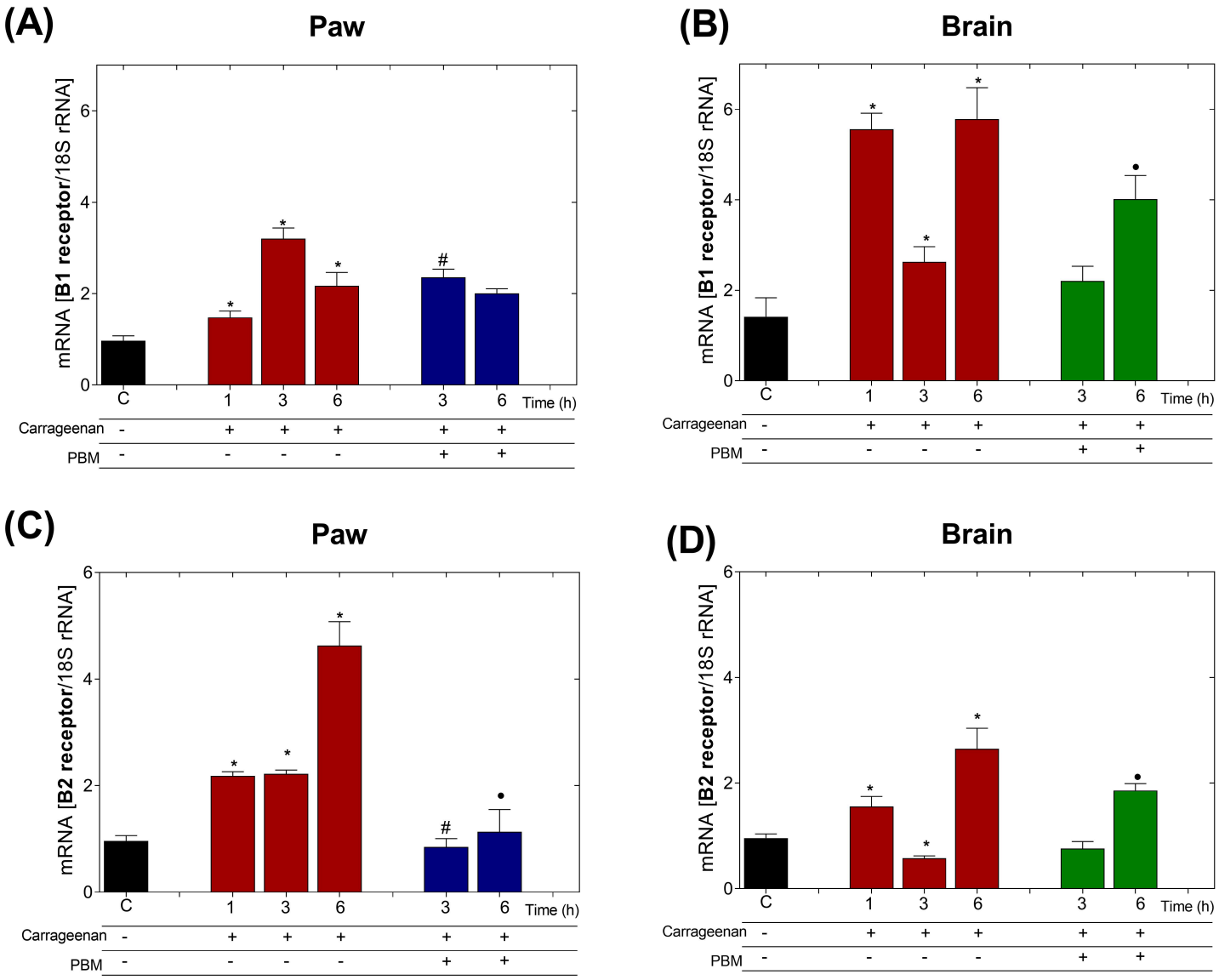


Figure 4

PBM differentially modulates the temporal expression of kinin B1 and B2 receptors in subplantar and total brain tissues. B1 receptor expression is presented for subplantar tissue (A) and total brain tissue (B), whereas B2 receptor expression is presented for subplantar tissue (C) and total brain tissue (D). In the paw, B1 receptor expression reached its highest level at 3 h, whereas B2 receptor expression showed its greatest increase at 6 h. In total brain tissue, both receptors exhibited time-dependent expression profiles and were significantly reduced by PBM at 6 h. Relative mRNA expression was determined by qRT-PCR using 18S rRNA as the reference gene. Data represent mean ± SD (n = 6 animals/group) and were analyzed by one-way ANOVA with the Tukey–Kramer post hoc test. Different symbols indicate significant differences ($p < 0.05$): *, versus the saline-treated control group; #, versus the carrageenan group at 3 h; and ●, versus the carrageenan group at 6 h. C, saline-treated control; PBM, photobiomodulation

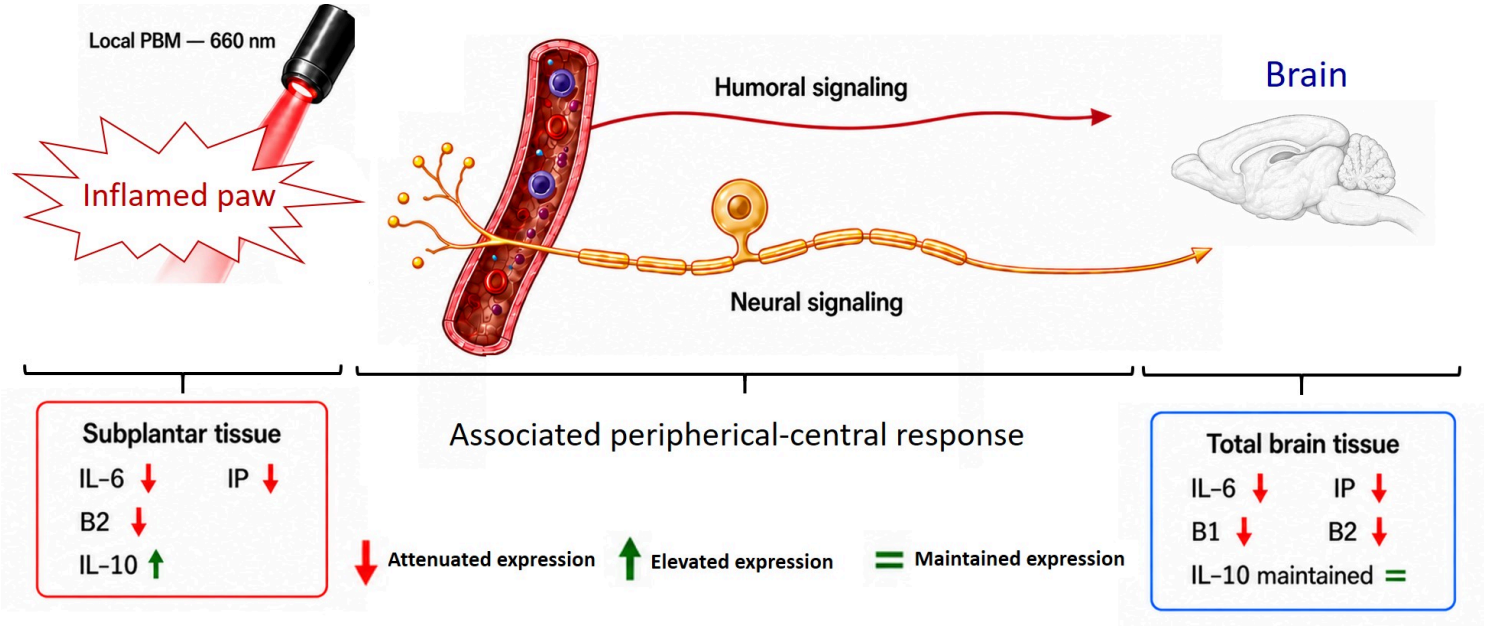


Figure 5

Integrated peripheral and central transcriptional responses associated with localized photobiomodulation following carrageenan-induced inflammation. PBM was applied locally to the inflamed paw 1 h after carrageenan administration. The schematic summarizes the responses observed at the final experimental time point, 6 h after inflammation induction, corresponding to approximately 5 h after PBM. At this time point, PBM attenuated IL-6, IP receptor, and kinin B2 receptor mRNA expression in subplantar tissue. Subplantar IL-10 mRNA expression remained elevated relative to the saline-treated control. In total brain tissue, PBM attenuated IL-6, IP receptor, and kinin B1 and B2 receptor mRNA expression, while IL-10 mRNA expression remained elevated. Humoral and neural signalling are depicted as plausible routes of peripheral–central communication but were not directly investigated in the present study. Downward arrows indicate attenuated mRNA expression, the upward arrow indicates elevated mRNA expression, and the equals sign indicates expression that remained elevated following PBM. PBM, photobiomodulation; IP, prostacyclin receptor; B1 and B2, kinin receptors