



PRÊMIO JOSÉ RIBEIRO DO VALLE 2013

O prêmio José Ribeiro do Valle, oferecido a cada ano pela SBFTE, visa identificar a cada ano os melhores trabalhos científicos desenvolvidos por jovens investigadores na área da Farmacologia. Entre os trabalhos inscritos para esta décima-quinta edição do prêmio, foram selecionados cinco finalistas, que fizeram apresentações de seus respectivos trabalhos perante comissão julgadora, em sessão pública durante o 45º Congresso Brasileiro de Farmacologia e Terapêutica Experimental, em Ribeirão Preto, SP. O resultado foi o seguinte:

Primeiro prêmio

Jaqueline Raymondi Silva

05.039 *Immune cell infiltration and production of inflammatory mediators in dorsal root ganglion, but not in spinal cord, are related to murine herpetic hyperalgesia.* Silva JR, Talbot J, Lopes AHP, Cunha TM, Cunha FQ FMRP-USP – Farmacologia

Introduction: Herpes Zoster (HZ) is a disease caused by the reactivation of latent herpesvirus Varicella Zoster (VZV) in the sensory ganglion, characterized by dermal rash and severe pain. VZV infects only humans, and there are no animal models available to study the disease. However, when mice are inoculated with herpes simplex virus type-1 (HSV-1) on the skin of the hind paw, they develop HZ-like skin lesions and show pain-related responses to noxious mechanical stimulation and innocuous tactile stimulus. For this reason, this model has been used to study the pathophysiology of herpes zoster. So far, there are no data available about the immune response in dorsal root ganglion (DRG) of mice infected with HSV-1 in this model, neither the relation between inflammatory response and hyperalgesia development. Thus, the aim of this study was to evaluate immune cells and inflammatory mediators present in DRGs and its relationship with herpetic hyperalgesia. **Methods:** Briefly, mice were depilated with a chemical depilatory and three days later 2×10^5 plaque forming unities (PFU) of HSV-1 were inoculated in the skin of the right hind paw after scarification. Mice were observed daily and behavioral tests were performed from 0-21 day post inoculation. The DRGs L1-L6 were collected at 7, 15 and 21 days post infection (dpi) to evaluation of cellular infiltration (flow cytometry), western blot analysis (GFAP and COX-2 expression) and PCR (TNF- α and COX-2 mRNA expression). Viral load was measured by quantitative Real-Time PCR. In some groups mice were treated with anti-TNF- α (1 μ g/i.t/day). All experiments were approved by the Animal Ethics Committee from FMRP/USP (nº 105/2010). **Results and Discussion:** Mice developed hyperalgesia from 3 to 21 dpi in the ipsilateral (ips) paws, but not in the contralateral (cl) paws. At 12 dpi all mice recovered from zoosteriform skin lesions. However, approximately 50% of mice showed persistent hyperalgesia behavior without zoosteriform skin lesions until 45dpi. A higher viral load was detected in DRGs L4, L5 and L6 of infected mice at 7 dpi, when compared to control or naive mice. We also observed an intense activation of satellite glial cells in ips DRGs (GFAP expression). Moreover, we observed, by flow cytometry, an intense inflammatory infiltrate composed by neutrophils and macrophages in ips DRGs but not in cl DRGs or spinal cord at 7dpi. Lymphocytes (CD4+ and CD8+) infiltration was detected at 15 and 21dpi in ips DRGs but not at the spinal cord. On infected mice, a higher mRNA expression of COX-2 and TNF- α was detected in ips DRGs. Moreover, blockage of TNF- α reduced de development of herpetic hyperalgesia. **Conclusions:** Our results show the presence of an intense inflammatory infiltrate in DRGs of infected mice, and the early expression of inflammatory mediators in this local that contribute for the induction of herpetic hyperalgesia. **Financial support:** FAPESP (2010/12309-8), FAEPA, TIMER.



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Segundo prêmio

Gabriela Trevisan

05.004 *TRPA1 receptor stimulation by hydrogen peroxide is critical to trigger pain and inflammation during acute gout attack.* Trevisan G¹, Hoffmeister C¹, Rossato MF¹, Oliveira SM¹, Silva MA¹, Silva CS¹, Nassini R², Materazzi S², Fusi C², Petri GP³, Geppetti P², Ferreira J⁴ ¹UFMS, ²University of Florence, ³UTFPR, ⁴UFSC

Introduction: Gout is the principal cause of inflammatory arthritis in men and postmenopausal women. However, the efficacy of the current treatments is still limited. Acute gout attacks are produced by articular deposition of monosodium urate (MSU) crystals and cause severe joint pain and inflammation, associated with oxidative stress. The transient potential receptor ankyrin 1 (TRPA1) is a sensor for oxidative substances (such as hydrogen peroxide - H₂O₂) found in peptidergic sensory fibers associated to inflammatory pain, but its role in gout is unknown. The goal of this study was to explore the TRPA1 participation in an experimental model of acute gout attack in rodents. **Methods:** Experiments were performed using male Wistar rats (200-250 g, N=5-8) bred in our animal house, and wild-type (*Trpa1*^{+/+}) or TRPA1 deficient mice (*Trpa1*^{-/-}) (25-30 g, N=7-10) (Jackson Laboratories, Italy). Protocols were approved by the Ethics Committee of the Federal University of Santa Maria (process number 108/2011(2)) or by the University of Florence (research permit number 204/2012-B). TRPA1 role in MSU intra-articular (i.a., ankle) injection-mediated inflammatory responses were evaluated using TRPA1 antagonists, defunctionalization of TRPA1 expressing fibers, and also TRPA1 genetic ablation of the TRPA1. TRPA1 expression, nociception, edema, plasma extravasation, neutrophil infiltration, interleukin 1 β (IL-1 β), H₂O₂ production or calcitonin gene-related peptide (CGRP) release were investigated after MSU i.a. injection. The possible activation of TRPA1 by H₂O₂ during the gout attack was also evaluated mimicking it with H₂O₂ or preventing it using H₂O₂-detoxifying enzyme catalase and the reducing agent dithiothreitol (DTT). **Results:** TRPA1 antagonism, gene ablation or sensory fiber defunctionalization largely reduced nociception, edema, neutrophil infiltration, plasma extravasation and IL-1 β increase caused by MSU i.a. injection. We have also observed that i.a. injection of MSU not only increased TRPA1 expression, but also CGRP release (an index of TRPA1 function) in MSU injected tissue. Besides inflammation, MSU also increased the level of H₂O₂ in the synovial tissue, but this effect was prevented by catalase and DTT. Finally, the signs of gout attacks were mimicked by i.a. injection of H₂O₂, and these effects were prevented by TRPA1 antagonism, gene ablation or sensory fiber defunctionalization. **Discussion:** Our results suggested that MSU i.a. injection increases tissue H₂O₂ thereby stimulating TRPA1 on sensory nerve endings to produce inflammation and nociception. Thus, the blockage of TRPA1 seems to be a useful target in acute gout attacks management.

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Menção Honrosa

Erika Cecon

04.032 *Amyloid beta peptide induces neuroinflammatory response in the pineal gland and impairs melatonin synthesis.* Cecon E¹, Fernandes PACM¹, Jockers R², Markus RP¹ ¹IB-USP, ² Institute Cochlin

Ana Carla Zarpelon

05.009 *Role of Interleukin-33/ST2 receptor signaling in chronic constriction injury-induced neuropathic pain in mice.* Zarpelon AC¹, Rodrigues FC¹, Carvalho TT¹, Souza GR², Ferreira SH², Alves-Filho JC², Liew FY³, Cunha TM², Cunha FQ², Verri WA Jr¹ ¹UEL – Departamento de Patologia, ²FMRP – Farmacologia, ³University of Glasgow – Immunology, Infection and Inflammation

Natália Tabosa Machado

06.025 *Nitric Oxide as a target for the hypotensive and vasorelaxing effects induced by (z)-ethyl 12-nitrooxy-octadec-9-enoate in rats.* Machado NT¹, Marciel PMP¹, Alustau MC¹, Queiroz TM¹, Furtado FF², Silva TAF¹, Vasconcelos WP¹, Santos PC¹, Oliveira-Filho AA¹, Veras RC¹, Araújo IGA¹, Athayde-Filho PF¹, Medeiros IA¹ ¹CCS-UFPB, ²CFP-ETSC-UFCG

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