PRÊMIO JOSÉ RIBEIRO DO VALLE – 2023

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 vigésima quinta edição do prêmio, foram selecionados cinco finalistas, que fizeram apresentações de seus respectivos trabalhos perante comissão julgadora, em sessão pública durante o 55º Congresso Brasileiro de Farmacologia e Terapêutica Experimental, realizado, no Hotel Rafain Palace & Convention, Foz do Iguaçu, PR. O resultado foi o seguinte:

Primeiro prêmio

Nathália Ferreira de Oliveira

01.003 **Crosstalk between Endothelial Purinergic P2Y2/P2X7 Receptors Increases Leukocyte Adhesion favoring Mesenteric Inflammation during Schistosomiasis**. Oliveira NF[1], Mainieri NS[1], Tamura AS[2], Coutinho-Silva R[2], Savio LEB[2], Silva CLM[1] [1]ICB-UFRJ, Brazil; [2]ICBBF-UFRJ, Rio de Janeiro Brazil

Introduction: The endothelial damage caused by chronic intravascular schistosomiasis promotes inflammation and ATP release, which modulates host immune responses through purinergic P2 receptors. Our previous data showed reduced levels of the endothelial P2X7R in the infected group compared to the control (Oliveira SDS., Purinergic. Signal., v.9 p.81, 2013). Since $P2Y_2R$ and P2X7R signaling favors inflammation, our aim was to investigate the role of endothelial $P2Y_2R$/P2X7R co-activation to schistosomal mesenteric inflammation in mice. **Methods**: Primary cultures of mesenteric endothelial cells (EC) were obtained from control (uninfected) and *Schistosoma mansoni*-infected mice (50-70 days p.i.; CEUA UFRJ 124/22) and used for Western blotting (WB), ELISA and leukocyte adhesion assays. Confluent EC were stimulated with UTP (1–300 µM) for 5h and/or with ATP 500 µM (30 min) in the presence or absence of antagonists or inhibitors (30 min pretreatment). Then, EC were co-incubated with isolated mononuclear cells (MC) (30 min), and then washed. Four fields/well were imaged to count the number of adherent MC (400X). Data were expressed as mean and SEM. **Results**: UTP (1–300 µM) increased MC adhesion to EC in a concentration-dependent manner in control and infected groups, but the maximal effect was higher in the infected (12.4 ± 0.6 cells/field) than in the control group (6.5 ± 0.3 cells/field, $P < 0.001$, Student´s t test, n= 5-6). Similar data were observed with 500 µM ATP ($P < 0.01$). Both the $P2Y_2R$ selective antagonist (ARC-118925 10 µM) or P2X7R antagonist (A740003 50 nM) blocked the respective agonist´s effect. In both groups, phospholipase C inhibitor (U73122 1 µM), intracellular Ca^{2+} chelator (BAPTA-AM 3 µM), SrC inhibitor (SU6656 5 µM) and VCAM-1 or ICAM-1 antibodies (1:50) impaired the UTP (100 µM) effect, corroborating the role of canonical and non-canonical $P2Y_2R$ signaling to leukocyte adhesion ($P < 0.01$). Of note, in the infected group U73122, BAPTA or VCAM-1 antibody not only blocked the UTP effect, but also decreased the basal MC adhesion (*i.e*. in the absence of agonist) suggesting that these EC have an enhanced Ca^{2+}-dependent VCAM-1-mediated pro-adhesive phenotype ($P < 0.001$).

However, WB data showed similar levels of $P2Y_2R$ expression. Regarding the putative receptors' crosstalk, in the infected group, the $P2Y_2R$ and P2X7R co-activation (100 µM UTP + 500 µM ATP) stimulated higher MC adhesion and IL-1β release than each agonist alone ($P < 0.01$). While in the infected group caspase inhibitor (z-VAD-FMK 20 µM) and NF-κB inhibitor (PDTC 3 µM) reduced the effect of ATP, UTP or both agonists, in the control group both inhibitors did not diminish MC adhesion. Moreover, the EC treatment with IL-1β (3 pg/mL) stimulated MC adhesion which was blunted by EC pretreatment with VCAM-1 antibody. Taken together, current data suggest that endothelial $P2Y_2R$/P2X7R crosstalk could be involved with mesenteric inflammation during schistosomiasis, with a putative role of inflammasome activation, IL-1β release and VCAM-1 expression. **Conclusion**: The mesenteric endothelial $P2Y_2R$/P2X7R co-activation increases leukocyte adhesion and downstream receptors signaling inflammasome-dependent releases IL-1β. Acknowledgments: FIOCRUZ (RJ), CNPq, CAPES, FAPERJ.

Segundo prêmio

Jorge Luiz Dallazen

05.015 **Analgesic Efficacy of the Slow-Releasing Hydrogen Sulfide (H_2S) Donor, GYY4137 and the Polysulfide, Dimethyl Trisulfide in Postoperative Pain Model: Role of Transient Receptor Potential Ankyrin 1**. Dallazen JL[1,2], Horváth AI[2,3], Tékus V[2], Hajna Z[2], Alsou'b DFB[2], Helyes Z[2,3,4], Pintér E[2,3,4], Costa SKP[1]. [1]ICB-USP, Dept Farmacologia, Brazil, [2]Dept Pharmacology and Pharmacotherapy, Medical School, University of Pécs, Hungary, [3]National Laboratory for Drug Research and Development, Budapest, Hungary, [4]Eötvös Loránd Research Network, Chronic Pain Research Group, University of Pécs, Hungary

Introduction: Postoperative pain affects about 80% of patients submitted to surgical intervention with few safe therapeutic options available (Gan TJ. J Pain Res, v10, p2287, 2017). The Transient Receptor Potential Ankyrin 1 (TRPA1) channel is activated by the slow-releasing H_2S donor (GYY4137) and polysulfide dimethyl trisulfide (DMTS), which in turn leads to analgesia via release of inhibitory mediators and/or sensory desensitization (Bátai IZ. Front Endocrinol, v9, p55, 2018). This study aimed to investigate the effects of GYY4137 and DMTS in a murine postoperative pain model with emphasis on the involvement of the TRPA1 channel. **Methods:** Plantar incision surgery (PIS) was performed in male C57BL/6, TRPA1-deficient (TRPA1 KO) and wild-type (TRPA1 WT) mice (8–12 weeks old; license BA02/2000-62/2022). Before and 24h after PIS, mechanonociceptive and thermonociceptive thresholds were determined by dynamic plantar aesthesiometry and hot plate, respectively, and paw volume by plethysmometry. Later, mice were intraperitoneally treated with GYY4137 (80, 260 and 800 µmol/kg), DMTS (80, 260 and 400 µmol/kg), or vehicle (VEH), and measurements were repeated 1, 3, and 5 h after treatments. The same parameters were measured in PIS-TRPA1 WT and KO mice using the effective dose of GYY4137 or DMTS and paralleled by detecting neutrophil myeloperoxidase (MPO) activity by *in vivo* luminescence imaging and blood perfusion by Laser Speckle. **Results:** PIS induced mechanical and thermal hyperalgesia, and paw edema in VEH-treated animals compared to the sham group. GYY4137 at 260 and 800 µmol/kg inhibited mechanical and thermal hyperalgesia compared to the VEH-treated group. DMTS at 400 µmol/kg reversed the mechanonociceptive threshold, without altering the thermonociceptive threshold at any tested dose. PIS-induced paw edema

was reduced by GYY4137 and DMTS in all tested doses. The analgesic effect of either GYY4137 (800 µmol/kg) or DMTS (400 µmol/kg) was absent in TRPA1 KO mice, but the anti-edematogenic effect was unaffected. The MPO activity in the operated paws of TRPA1 KO mice was significantly lower as compared to TRPA1 WT mice. Whilst GYY4137 treatment reduced the increased MPO activity in operated paw of TRPA1 WT mice, it further enhanced MPO activity in TRPA1 KO mice. DMTS reduced MPO activity in TRPA1 WT mice, without affecting this parameter in TRPA1 KO mice. TRPA1 WT and KO mice exhibited increased blood perfusion in the operated paw, which were restored to the basal levels by GYY4137 and DMTS. **Conclusion:** The analgesic effects of GYY4137 or DMTS are modulated by the TRPA1 channel, whilst the anti-inflammatory actions are not. **Financial support:** CAPES (001); CNPq (142343/2020-0; 200357/2022-0; 312514/2019-0); Hungarian research grants EGA-16; Eötvös Loránd Research Network; Hungarian Brain Research Program-3; National Laboratory of Drug Research and Development.

Menção Honrosa

Bruna Felippe Ferreira

- 03.023 **Antagonism of TRPV1 Receptors Associated with FAAH Inhibition is Necessary to Facilitate the Impaired Fear Extinction in iNOS Knockout Mice**. Ferreira BF[1], Sato Y[1], Marques APA[1], Fronza MG[1], Lisboa SFS[2]. [1]USP, Dpt of Pharmacology, Ribeirão Preto, Brazil, [2]USP, Dpt of Biomolecular Sciences, Ribeirão Preto, Brazil

Bianca de Sousa Leal

- 10.011 **Activity of the Cysteine Protease cms2ms3 and the Vla-4 Integrin Role in Stages of b16f10 Melanoma Metastasis**. Leal BS[1], Ferreira LPF[1], Menezes DP[1], Lopes MTP[2], Sousa JMC[3], Ferreira PMP[1], Dittz D[1] [1]UFPI PPG Pharmacology, Brazil; [2]UFMG Pharmacology, Brazil; [3]UFPI PPF Pharmaceutical Sciences

Gabriela Gomes Ferreira

- 04.023 **Supression by Gold Nanoparticles (AuNPs) of Lung Fibrosis Target by Bleomycin in Mice**. Ferreira, GG; Guimarães, FV1; Fernandes, AJM; Pires, ALA; Arantes, ACS; Janinni-Sá, YAP; Martins, MA; Silva, PMR. IOC-Fiocruz, Laboratory of Inflammation. RJ, Brazil

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