



PRÊMIO JOSÉ RIBEIRO DO VALLE 2015

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-sétima edição do prêmio, foram selecionados cinco finalistas, que fizeram apresentações de seus respectivos trabalhos perante comissão julgadora, em sessão pública durante o 47º Congresso Brasileiro de Farmacologia e Terapêutica Experimental, em Aguas de Lindóia, SP. O resultado foi o seguinte:

Primeiro prêmio

Daniele Maria Ferreira

09.001 Rhamnogalacturonan as a potential therapeutic target for the treatment of ulcerative colitis. Maria-Ferreira D¹, Borato DG¹, da Silva LM, Corso CR¹, Nascimento AM², Cipriani TR², Watanabe PS³, Santana DMG³, van den Wijngaard RM, Werner MFP¹, Baggio CH¹ ¹UFPR – Farmacologia, ²UFPR – Bioquímica, ³UEM

Introduction: Ulcerative colitis is a chronic disorder that affects the colon with unknown etiology. Despite several treatment options, not all patients are responsive to therapy and their use is related with side effects. Taking into account, the polysaccharides recently became the focus of studies exhibiting important pharmacological activities as immunomodulatory and antinociceptive. In addition, our group already showed that the polysaccharide rhamnogalacturonan (RGal) isolated from *Acmella oleracea* has potent antiulcerogenic and gastric ulcer healing activities (Maria-Ferreira *et al.*, Plos One, v. 9, p. e84762, 2014). Therefore, in this study we investigate the protective effects of RGal in the dextran sulfate sodium (DSS)-induced colitis in mice and the underlying mechanisms in heterogeneous human epithelial colorectal adenocarcinoma cells (Caco-2). **Methods:** Colitis was induced by administration of DSS for 5 days followed by 2 days of water. The animals were orally treated with vehicle (water, 1 ml/kg) or RGal (10 mg/kg) daily. Colitis characteristics (body weight change, presence of blood in feces and fecal consistency) were monitored daily, and visceral allodynia was evaluated by von Frey filaments. After 7 days, the colons were collected and their weight and length were measured. The colonic tissues were used for the enumeration of total neurons of the myenteric plexus and histological evaluation. Caco-2 cells were challenged with IL-1 β in a transwell epithelial cellular permeability assay and were used for analysis of IL-8 levels and also expression and distribution of tight junction proteins claudin-1, occludin and ZO-1 by immunoblot or immunofluorescence (CEUA/BIO-UFPR; approval number 721). **Results and Discussion:** The treatment with RGal reduced the colitis score from the day 5 (28%) to the day 8 (46%), protected mice from body weight loss (day 8, 51%) and reduced the macroscopic damage when compared to the DSS group. RGal also prevents the reduction of colon length (RGal: 9.1 \pm 0.2 cm) when compared to DSS group (DSS: 7.1 \pm 0.2 cm), reduced the withdrawal response to mechanical stimulation of the abdomen by von Frey hairs and protected the colonic ganglion cells when compared to the DSS group. In histological analysis, RGal increased mucosal and submucosal thickness in 22 and 54% and decreased the thickness of the muscular layer and total wall in 38 and 18% respectively when compared to the DSS group accompanied by the maintenance of mucosal enterocytes and goblet cells. In the transwell assay, RGal (100 and 1000 μ g/ml, inner well) prevented the cellular permeability in 43 and 65%, respectively, and 77% at 1000 μ g/ml (outer well), when compared to IL-1 β group. We also observed a



PRÊMIO JOSÉ RIBEIRO DO VALLE 2015

significantly reduction of IL-8 secretion (RGal: 807 ± 49.7 pg/ml) and a diminished claudin-1 expression (40%) when compared to IL-1 β group. **Conclusion:** Collectively, we demonstrated that RGal reduces the severity of DSS colitis in mice through protecting colon epithelium and neurons of the myenteric plexus, reducing the abdominal allodynia, epithelial permeability and cytokine secretion and maintaining the integrity of junction complexes. Thus, RGal may represent a promising molecule for drug development to the treatment of ulcerative colitis. **Support:** CAPES, CNPq, Nuffic

Segundo prêmio

Andrea Rodrigues Vasconcelos

01.002 Age-related adaptive effects of intermittent fasting during neuroinflammation. Vasconcelos AR¹, Yshii LM¹, Kinoshita PF¹, Böhmer AE¹, Orellana AMM¹, de Sá Lima L¹, Alves R¹, Andreotti DZ¹, Marcourakis T¹, Viel TA¹, Buck HS², Mattson MP³, Scavone C¹, Kawamoto EM¹ ¹USP, ²Santa Casa de São Paulo, ³NIH

Introduction: Neuroinflammation is a common characteristic of neurodegenerative disorders that may contribute to loss of function and cell death. Sepsis induced by lipopolysaccharide (LPS) causes neuroinflammation and results in enduring cognitive impairment which is a risk factor for dementia. There are currently no effective treatments for infection-induced cognitive impairment. Previous studies showed intermittent fasting (IF) can increase the resistance of neurons to disease by stimulating adaptive cellular stress responses. However, the impact of IF on the cognitive sequelae of inflammation is unknown. Moreover, LPS signaling is linked to nitric oxide (NO)-Na,K-ATPase pathway in the central nervous system (CNS). IF can suppress inflammation, but the age-related effects of IF on LPS modulatory influence on NO-Na,K-ATPase pathway are unknown. Aims: This work evaluated whether IF might modify the adverse effects of systemic inflammation induced by LPS on cognitive function. Also, it was investigated the effects of IF on age-related changes on the activity of $\alpha_1, \alpha_{2,3}$ -Na,K-ATPase and oxidative status induced by LPS in rat hippocampus. **Methods:** 4 month-old (mo) Wistar rats on IF for 30 days received LPS (1mg/kg) or saline intravenously. Half of the rats were subjected to behavioral tests (open field, rotarod, Barnes maze and inhibitory avoidance) and the other half were euthanized two hours after LPS administration and the hippocampus was dissected and frozen for analyses of inflammatory parameters (cytokines and brain-derived neurotrophic factor (BDNF) levels, RelA nuclear protein expression, nuclear factor κ B (NF- κ B) binding activity, toll-like receptor (Tlr)-4 (LPS receptor) and inducible NO synthase (iNos) mRNA levels. Moreover, young (4-mo), adult (12-mo), and aged (24-mo) rats were submitted to the same protocol and the hippocampus was dissected for measurements of $\alpha_1, \alpha_{2,3}$ -Na,K-ATPase activity, NOS gene expression and/or activity, cyclic GMP, 3-nitrotyrosine (3-NT)-containing proteins, and thiobarbituric acid reactive substances (TBARS). Results: LPS treatment resulted in cognitive deficits in the Barnes maze and inhibitory avoidance task which were ameliorated in rats that were subjected to the IF protocol, with no changes in locomotor activity. IF also: prevented or attenuated LPS-induced elevation of cytokines, iNos and Tlr4 levels in hippocampus and/or serum; prevented LPS-induced BDNF reduction in hippocampus; blocked or mitigated the age-related decline of cGMP and Na,K-ATPase activity, and the increase of iNos gene expression, TBARS, and 3-NT proteins in the presence or absence of LPS. **Conclusion:** Taken together, our results suggest that IF induced adaptive responses in the brain and periphery that can suppress inflammation and preserve cognitive



PRÊMIO JOSÉ RIBEIRO DO VALLE 2015

function in an animal model of sepsis. Therefore, IF could reduce the risk for brain function deficits and neurodegenerative disorders linked to inflammatory response in the CNS during aging. **Financial Support:** FAPESP, CNPq. All procedures were approved by the Biomedical College of Animal Experimentation and the Ethical Committee for Animal Research ICB/USP (89 fls. 60, book 02).

Menção Honrosa

Raquel Dal Sasso Freitas

05.002 Pre-clinical evidence on the benefits of docosahexanoic acid on adverse and anti-tumoral effects of cyclophosphamide. Freitas RDS^{1,2}, Costa KM^{2,1}, Nicoletti NF^{2,1}, Campos MM^{3,2,1} ¹PUCRS – Toxicologia e Farmacologia, ²PUCRS – Medicina e Ciências da Saúde, ³PUCRS – Odontologia

Juliana Florenzano

04.003 Increased TRPA1 mRNA expression and antioxidant enzymes activity may contribute to sex differences in pulmonary allergic inflammation in young mice prior exposed to ambient pollutant 1,2-naphthoquinone. Florenzano J, Santos KT, Feitosa KB, Soares AG, Rodrigues L, Teixeira SA, Muscará MN, Costa SKP ICB-USP – Farmacologia

João Francisco Cordeiro Pedrazzi

03.001 Cannabinoids compounds attenuate sensorimotor gating disruption induced by amphetamine in mice. Pedrazzi JFC¹, Issy AC², Gomes FV³, Guimarães FS³, Del Bel EA² ¹FMRP-USP – Neurociências e Ciências do Comportamento, ²FORP-USP – Fisiologia, Morfologia e Patologia Básica, ³FMRP-USP – Farmacologia

Comissão Julgadora

Frederico G. Graeff (USP, coordenador)

Daniela de Almeida Cabrini (UFPR)

Geanne Matos de Andrade (UFC)

Patrocinadora do Prêmio José Ribeiro do Valle

BiOLAB
FARMACÊUTICA