PRÊMIO JOSÉ RIBEIRO DO VALLE 2017

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-nona edição do prêmio, foram selecionados cinco finalistas, que fizeram apresentações de seus respectivos trabalhos perante comissão julgadora, em sessão pública durante o 49º Congresso Brasileiro de Farmacologia e Terapêutica Experimental, em Ribeirão Preto, SP. O resultado foi o seguinte:

Primeiro prêmio

Fernando Olinto Carreño

11.001 ***Lipid core nanocapsules modulate quetiapine hippocampal exposure in a neurodevelopmental model of schizophrenia.*** Carreño F[1], Helfer VE[1], Staudt KJ[1], Paese K[1], Meyer FS[1], Silva CM[1], Herrmann AP[2], Rates SMK[1], Guterres SS[1], Dalla Costa T[1] [1]UFRGS, [2]UFFS

Introduction: High variability in chronic schizophrenia (SCZ) response to treatment may be partially related to blood-brain barrier (BBB) dysfunction caused by the disease[1]. Neurodevelopmental model of SCZ induced by administration of viral mimic polyinosinic–polycytidilic acid (poly i:c) to pregnant rats has substantial face validity. Adult offspring demonstrate sensorimotor gating deficits, enhanced sensitivity to MK-801 hyperlocomotion and morphofunctional alterations in the hippocampus that parallels SCZ neuropathology opening new opportunities for the investigation of better treatments[2]. This study aimed to investigate free and nanoencapsulated quetiapine (QTP) neuropharmacokinetics in a neurodevelopmental model of SCZ. **Methods:** Protocols approved by UFRGS' Ethics Committee in Animal Use (#31001). Pregnant Wistar dams (GD15) received poly (i:c) 4 mg/kg i.v. *bolus* dose. SCZ-like deficits in the adult offspring (PND75) were confirmed by elevated plus-maze, pre-pulse inhibition of the startle response and MK-801 induced hyperlocomotion (*P* groups). QTP lipid core nanocapsules (QLNC, 1 mg/mL) were obtained by nanoprecipitation[3]. Hippocampal implantation[3] of microdialysis probes (CMA 12, 3 mm PAES, 20 kDa cutoff) was used to access active unbound QTP concentrations and jugular vein was cannulated for blood sampling. PK was evaluated in awaken animals after single i.v. dosing of QTP solution (FQ-*P*, 10 mg/kg, n = 5) or QLCN-*P* (5 mg/kg, n = 5) 48 h after brain surgery. Control naive offspring groups (*N* groups) received QTP solution (FQ-*N*, 10 mg/kg; n = 7) or lipid core nanocapsules (QLNC-*N*, 5 mg/kg, n = 6). PK parameters determined using Phoenix® v. 64 software. **RESULTS:** Groups that received QLNC showed increased half-life (QLNC-*N* = 3.7 ± 1.0 h and QLNC-*P* = 5.4 ± 2.4 h) in comparison to groups that received QTP solution (FQ-*N* = 2.9 ± 0.8 h and FQ-*P* = 3.8 ± 1.1 h) due to a significant decrease in clearance (QLCN-*N* = 0.8 ± 0.1 L/h/kg; QLNC-*P* = 0.6 ± 0.1 L/h/kg; FQ-*N* = 1.6 ± 0.2 L/h/kg; FQ-*P* = 1.4 ± 0.4 L/h/kg) ($p<0.05$). Volume of distribution was not altered due to nanoencapsulation. Unbound hippocampal exposure to QTP ($AUC_{0\text{-}8h}$/D) in naive offspring was similar for QTP in solution and QLCN (FQ-*N* = 0.20 ± 0.05 and QLCN-*N* = 0.24 ± 0.04). However, the significant

decrease in hippocampal exposure in FQ-*P* group (0.11 ± 0.01) was reverted by drug nanoencapsulation (QLNC-*P* = 0.24 ± 0.02) ($p<0.05$). **Conclusions:** QTP brain exposure is reduced in SCZ-induced rats, supporting the hypothesis that BBB dysfunction contributes to treatment failures. Drug encapsulation on lipid core nanocapsules overcomes BBB disorder, returning drug penetration to the levels observed in normal animals. **References:** [1] Schoknecht, K. et al. Epilepsia. 53, 7-13, 2012. [2] Macedo et al Braz J Med Biol Res. 45(3): 179–186, 2012. [3] Carreño, F. et al. Mol. Pharm. 13, 1289, 2016. **Acknowledgments:** Financial support CNPq/Brazil and CAPES- PROEX 646-2014.

Segundo prêmio

Ana Elisa Gonçalves

02.010 ***Evaluation of anti-Alzheimer effects of tacrine dimers in animals with peptide Aβ1-42-induced Alzheimer.*** Gonçalves AE[1], Mariano LNB[1], Silva LM[1], Aquino RAN, Fatima A[2], Andrade SF[1], Souza MM[1]
[1]Univali – Ciências Farmacêuticas, [2]UFMG – Química

Introduction: Alzheimer's Disease (AD) is the leading cause of dementia in the world. It is a neurodegenerative disease that causes progressive cognitive impairment. The typical brain lesions in patients with AD are extracellular β-amyloid peptide deposits, as well as the presence of neurofibrillary tangles. Patients also present neuroinflammation and alterations of the oxidative system. Currently, the treatment available for AD includes inhibitors of cholinesterase enzymes and an NMDA receptor antagonist (N-methyl D-Aspartate). These drugs are palliative and only improve patients' cognition, but they do not help to reduce progression of the disease. The aim of this work is to investigate the effect of new tacrine dimers on mice with amyloid peptide ($A\beta_{1-42}$) induced DA, using in vivo behavioral tests and ex vivo oxidative system analysis, and to evaluate possible hepatotoxic effects in animals treated for 15 days. **Methods:** To evaluate the effect of the treatment on the locomotor and exploratory system in animals, the Open Field test was used, and different types of animal memory were analyzed through the Object Recognition (OR), Inhibitory Avoidance (IA) and Morris Water Maze (MWM) tasks. In relation to the effect of treatments on the oxidative and neuroinflammatory system in the cortex and hippocampus of the animals, the levels of reduced glutathione (GSH), superoxide dismutase (SOD) and myeloperoxidase (MPO) and the levels of Lipid hydroperoxide (LOOH) were determined. The effect of treatment on the hepatic system was analyzed by the measurement of transaminases (AST and ALT) in the serum of the animals and histological analysis of the liver, as well as the effect of the dimers on the cytotoxic activity in human hepatoma cells (HepG2). **Results:** All dimers studied (DT1, DT2, DT3 and DT4), which are known to be cholinesterase inhibitors, showed improvement of the cognitive deficit caused by the $A\beta_{1-42}$ peptide in the OR, IA and MWM tasks. DT4 dimer showed decreased locomotion in the Open Field test, as did tacrine itself. Regarding the oxidative system analyzes, all the dimers presented improvement in the levels of GSH in the hippocampus. SOD activity remained decreased with the DT2, DT3 and DT4 dimer treatments. All dimers showed a decrease in MPO activity. Only the DT4 dimer was able to reduce the levels of LOOH. In relation to the hepatic system, DT1 and DT3 dimers raised AST levels as well as tacrine, data confirmed by histological analysis of the liver of the animals. DT2 and DT4 dimers appear to be the ones with the lowest hepatic lesion. No dimer presented cytotoxicity in HepG2 cells. **Conclusion:** The results suggest that the dimers studied show improved cognition of animals with $A\beta_{1-42}$ induced AD, as well as other additional neuroprotection effects. The results also correspond to the DT2 dimer as a promising pharmacological target for the treatment of AD. **Financial support and acknowledgments:** CAPES and UNIVALI. Process number of Ethics Committee on Animal Use - CEUA / UNIVALI: 11/16.

Menção Honrosa

Bruno Marcel Silva de Melo

04.026 ***The alarmin S100A9: A key target for treatment of psoriasis***. Melo B[1], Protasio F[1], Prado D[1], Costa L[2], Souza C[2], Lima D[3], Nakaya H[3], Cunha T[1], Cunha F[1], Alves-Filho JC[1] [1]FMRP-USP – Farmacologia, [2]FMRP-USP, [3]FCF-USP – Análises Clínicas e Toxicológicas

Bryelle Eccard de Oliveira Alves

06.008 ***Novel DPP4 inhibitor reduces cardiac and vascular dysfunction induced by diabetes Type 2 in rats***. Eccard B[1], Reina E[1], Araújo JSC[1], Barreiro EJ[1], Lima LM[1], Trachez MM[2], Sudo RT[1], Zapata-Sudo G[1] [1]UFRJ, [2]UFF

Lucas Antonio Duarte Nicolau

08.002 ***Promising therapeutic approach in GERD: Topical protection to oesophageal mucosa and anti-inflammatory outcome of a biopolymer in mice and human biopsies***. Nicolau LAD[1,2], Batista-Lima FJ[1], Santana AP[1], Sales TM[3], Oliveira TM[4], Medeiros JVR[4], Silva DA[4], Vale ML[1], Nobre-e-Souza MA[3], Santos AA[1], Sifrim D[2], Souza MHP[1] [1]UFC – Fisiologia e Farmacologia, [2]Queen Mary University of London – Neurogastroenterology, [3]UFC – Ciências Médicas, [4]UFPI – Biotecnologia

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