PRÊMIO JOSÉ RIBEIRO DO VALLE 2010

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-terceira edição do prêmio, foram selecionados cinco finalistas, que fizeram apresentações de seus respectivos trabalhos perante comissão julgadora, em sessão pública durante o 42º Congresso Brasileiro de Farmacologia e Terapêutica Experimental, em Ribeirão Preto, SP. O resultado foi o seguinte:

Primeiro prêmio

Vanessa Olzon Zambelli

05.028 Peripheral sensitization increases opioid receptor activation and expression in both dorsal root ganglia and nerve paw of rats. Zambelli VO[1], Gutierrez VP[1], Fernandes ACO[1], Parada CA[2], Cury Y[1] [1]IBu − Dor e Sinalização, [2]UNICAMP – Farmacologia

Introduction: Besides their central mechanisms of action, opioids also exert analgesia through peripheral mechanisms. This peripheral action allows for analgesia after application of systemically inactive doses of opioids directly into injured peripheral tissue, minimizing adverse central effects. Several data have shown that the peripheral efficacy of opioid drugs is enhanced in the presence of tissue injury, but the mechanisms involved in this phenomenon are not well known. Previous data of our group showed that, in rats, prostaglandin E2 (PGE2, intraplantar/i.pl.) and chronic constriction injury (CCI) of sciatic nerve increase the peripheral analgesic efficacy of opioid agonists and of crotalphine (CRP), a peptide obtained from C. d. terrificus snake venom. CRP induces peripheral analgesia mediated by activation of k- opioid receptor in PGE2-induced hyperalgesia or k- and d- opioid receptor in CCI model. This study aims to characterize some of the mechanisms involved in the increase of the analgesic efficacy of opioids caused by inflammation/tissue injury. For this purpose the effect of PGE2-induced hyperalgesia and CCI on opioid receptor expression and activation in dorsal root ganglia (DRG) and nerve paw (NP) of male Wistar rats was evaluated. **Methods:** Expression and activation of opioid receptors were evaluated by rt-PCR, immunoblotting and ELISA assays, 3h after i.pl. injection of PGE2 (100 ng/paw) or 14 days after CCI. In vitro studies were carried out in DRG cell culture incubated with PGE2 and/or opioid agonists (1 mM). The protocols were approved by the Butantan Institute Ethical Committee (386/07). **Results:** PGE2 increases genic and proteic expression of m − and k-opioid receptors in NP (43% and 71%, respectively) and decreases (30%) the expression of d-opioid receptors, when compared to naïve rats. m-opioid receptor expression is also increased in the ipsilateral and contralateral DRG (79 and 27%, respectively), while k-opioid receptor expression is increased only in the ipsilateral DRG (168%). CCI up-regulates m-opioid receptors in NP (27%) and DRG (ipsi and contralateral, 49 and 20%, respectively) and d-opioid receptors in DRG (ipsilateral, 35%). In contrast, k-opioid receptors are down-regulated by CCI in NP (51%) and DRG (21%). Despite the increase in receptor expression, PGE2 did not cause receptor conformational changes. Activation of m- and k-opioid receptors was observed after treatment with CRP or opioid agonist. The activation caused by CRP or opioid agonist was enhanced in NP slices under PGE2 (16 and 20%, respectively) or CCI sensitization (15 and 30%, respectively) or DRG cells incubated with PGE2 (43 and 45%, respectively). **Discussion:** The results indicate that peripheral opioid receptor expression and activation are distinctly regulated by the presence of acute or chronic injury. The different pattern of k and d opioid receptors expression caused by acute and chronic injury may contribute to the activation of distinct opioid receptors by CRP, in the presence of PGE2 and CCI. These data also point out that drugs that activate peripheral opioid receptors, including substances derived from animal toxins, might have therapeutic potential as peripherally analgesics. Support: FAPESP, INCTTOX Program

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Segundo Prêmio

Amanda Juliana Sales

03.015 DNA demethylating agents: new antidepressant drugs? Sales AJ[1], Biojone C[2], Gomes MVM[3], Joca SRL[1] [1]FCFRP-USP − Física e Química, [2]FMRP-USP − Farmacologia, [3]UNOPAR − Genética

Introduction: Recent evidences have suggested that epigenetic mechanisms are thought to play a role in the plastic and behavioral changes induced by stress and antidepressant drugs. For example, histone acetylation, which is associated with transcriptional activation of specific genes, is increased in the hippocampus after chronic antidepressant treatment, what is thought to account for their therapeutic effects. On the other hand, DNA methylation, which is associated with transcriptional repression, is increased by stress exposure. Moreover, higher levels of methylation at specific genomic loci have been found in the hippocampus of suicide victims. Despite that, the direct involvement of DNA methylation in the regulation of depressive-like behaviors has not been investigated yet. Therefore, the aim of the present study was to test the hypothesis that DNA demethylation and the subsequent increase in gene expression would induce antidepressant-like effects. The effects induced by systemic or intra-hippocampal administration of different DNA demethylating agents (decitabine and 5-azacytidine) were then investigated in rats submitted to an animal model of depression, the forced swimming test (FST). **Methods:** Male Wistar rats (8-9/group) were submitted to a forced swimming pretest (PT) and received 3 ip injections (0, 5 and 23h later) of decitabine (0.1, 0.2, 0.3, 0.4 mg/kg), 5-AZA (0.4, 1.6, 3.2 mg/kg), imipramine (15 mg/kg) or vehicle. 24h after PT, the immobility time was registered at a 5 min swimming test. An independent group of animals underwent the same behavioral and pharmacological manipulations but were submitted to the open field test in order to assess drug-induced unspecific locomotor changes. A third group of rats (n= 6-8/group) were submitted to PT and received an intra-hippocampal injection of decitabine (50, 100 or 200 nmol/0.5 uL) or saline and were submitted to the test 24h later. After the behavioral tests, the hippocampus was removed for further analysis of the genomic DNA methylation (quantification of 5-methyl-2-deoxy cytidine using an ELISA kit). All behavioral protocols described herein were approved by our local ethical committee (CEUA, 10.1.136.53.2). **Results:** Systemic treatment with decitabine or 5-AZA reduced the immobility time in the forced swimming test ($F_{7,52}=8.19$, $P<0.01$; $F_{4,33}=10.86$, $p<0.01$; respectively), in a dose dependent fashion, similarly to the prototype antidepressant imipramine. Decitabine microinjection into the hippocampus also induced antidepressant-like effect, at the dose of 100 nmol/0.5 uL ($F_{3,28}=3.6$, $p<0.05$; Dunnets, $p<0.05$). None of the treatments induced significant locomotor effects in the open field test. The genomic DNA methylation profile in the hippocampus is under investigation. **Conclusion:** The present results indicate that the treatment with DNA demethylating agents induces antidepressant-like effects, similarly to imipramine. Therefore, DNA methylation might constitute an important pharmacological target for new antidepressant drugs. The results also point to the hippocampus as a structure where stress-induced DNA methylation might regulate depressive like-behaviors and contributes to a better comprehension about the neurobiology of depression. **Financial Support**: FAPESP, CNPq.

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Menção Honrosa

Larissa Staurengo Ferrari

05.009 IL-33 receptor deficiency reduces inflammation in septic arthritis in mice. Staurengo-Ferrari L[1], Cardoso RDR[1], Xu D[2], Liew FY[2], Cunha FQ[3], Pelayo JS[4], Saridakis HO[4], Verri Jr WA [1] [1]UEL − Ciências Patológicas, [2]University of Glasgow − Immunology Infection, Inflammation, [3]FMRP-USP, [4]UEL − Microbiologia, [6]UEL − Ciências Patológicas

Eduardo Moreira de Oliveira

02.052 Relationship of long-term memory evocation and cholinergic markers in hippocampus, along the aging process of rats. Oliveira EM[1], Souza LHJ[1], Schowe NM[1], Albuquerque MS[1], Baraldi T[1], Chambergo FS[1], Pina dos Santos VP[2], Araújo MS[2], Buck HS[3], Viel TA[1] [1]EACH-USP, [2]UNIFESP − Bioquímica, [3]FCMSCSP − Ciências Fisiológicas

Narayana Fazolini P. Bastos

10.014 Leptin activates the mTOR pathway in epithelial cells: roles in lipid metabolism, inflammatory mediator production and cell proliferation. Bastos NFP[1], Viola JPB[2], Maya-Monteiro CM[1], Bozza PT[1]. [1]IOC-FIOCRUZ − Imunofarmacologia, [2]INCa – Cellular Biology

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