03. Psychopharmacology

03.001 Psychopharmacological effects of N-acetylcysteine in Zebrafish. Mocelin R[1], Herrmann AP[2], Marcon M[1], Rambo AL[3], Abreu MS[4], Zanatta L[5], Elisabetsky E[6], Barcellos LJG[7], Lara DR[3], Piato AL[6] [1]UFRGS – Neurociências, [2]UFFS, [3]PUCRS – Biologia Celular e Molecular, [4]UFSM – Farmacologia, [5]UNOCHAPECO – Ciências Ambientais, [6]UFRGS – Farmacologia e Terapêutica, [7]UPF – Bioexperimentação

Introduction: Anxiety disorders have high prevalence and may cause significant impacts on the quality of life. Despite the recent advances in understanding the pathophysiology of anxiety disorders, the pharmacological treatments currently available are limited in efficacy and induce serious side effects. A possible strategy to achieve clinical benefits is drug repurposing, i.e., discovery of new applications for old drugs. Considering the role of N-acetylcysteine (NAC) as a modulator of neurotransmitter systems related to psychopathologies, we evaluated the effects of exposure to NAC on behavioral parameters in zebrafish. **Methods:** Zebrafish were exposed to Control (water), NAC (0.1, 1.0 and 10.0 mg/L), fluoxetine (FLU 10.0 mg/L) or bromazepam (BMZ 1.5 mg/L) for 10 minutes. After treatment, different sets of animals were individually subjected to the following behavioral tests: (1) novel tank (6 min), (2) acute stress model – chasing with a net (2 min) or (3) light-dark (5 min). Videos were recorded and latter analyzed by the ANY-Maze software (Stoelting Co., USA). Results were analyzed by one or two ways ANOVA followed by Tukey post-hoc (n=12-15). **Results:** In the novel tank test, NAC did not change any behavioral parameters evaluated, while fluoxetine significantly increased time in the upper portion of the tank ($p<0.01$ x control). In the second protocol, we evaluated the effects of NAC in an acute stress model. NAC prevented the behavioral changes induced by acute stress on distance moved and time spent in the bottom, middle zone and upper zones. In the third protocol, zebrafish were to the light-dark test. NAC significantly increased the time spent in the light side of the apparatus compared to control animals ($p<0.05$). This effect was comparable to bromazepam. **Conclusion:** The results of this study demonstrated for the first time that NAC has anti-stress properties and anxiolytic-like effects in zebrafish, supporting its potential to prevent stress-induced psychiatric disorders such as anxiety and depression. The mechanism of action of this drug involves modulation of antioxidant, inflammatory, neurotrophic and glutamate pathways. The exact mechanisms that contributed to the effects observed in this study remain to be elucidated. More studies are needed to investigate the possible use of NAC in the treatment of psychopathologies. **Human or Animal Research Ethical Committee:** Nº 30914/UFRGS **Financial support:** CNPq (472715/2012-7).

03.002 Combined use of alcohol and tobacco on behavioral and neuroinflammatory parameters in rats. Bandiera S[1], Pulcinelli RR[2], Giustina CLD[2], Hansen AW[1], Caletti G[1], Souza A[1], Medeiros LF[1], Torres ILS[1,3], Gomez R[1,3] [1]UFRGS – Farmacologia e Terapêutica, [2]UFRGS, [3]UFRGS – Farmacologia

Introduction: Alcohol and cigarettes are drugs frequently used in combination. Although reduction of psychoactive effects of one (depressant) or other drug (stimulant) may justify increasing on the prevalence of the combined use, few studies explore if neuroinflammation could influence this behavior. The relationship between cognitive impairment and behavioral changes by chronic use of alcohol and neuroinflammation are known, but there are no studies evaluating these parameters by chronic use of tobacco or its association with alcohol. Therefore, our objective was to evaluate the effect of chronic administration of the combined use of alcohol and cigarette smoke on behavioral and inflammatory parameters in rats. **Methods:** Male, adults, Wistar rats (n = 48) were divided into ALC group, treated with 2 g/kg alcohol, intragastrically (IG); TBC group, exposed to the smoke of 6 cigarettes, for 2 h; ALTB group, association between 2g/kg alcohol, IG, and smoke of 6 cigarettes; and CTR group (water, IG). They were treated twice a day, for 28 days. On the day 20, after 1 h from the onset of treatment, the animals were placed in the open field test (100□100□50 cm) and assessed to the total and central crossings, rearing and grooming, as well as time of rearing and grooming. In the day 28 animals were sacrificed, and the frontal cortex (FC), hippocampus (HP) and striatum (ST) were dissected for interleukins dosages (IL-1□, IL-10 and TNF-□), by ELISA. **Results:** Analysis of variance (ANOVA) showed by the 2-way showed that ALC, TBC, and ALTB increased the central and total crossing compared with CTR group (total crossing: CTR: 103.1 ± 5.7; ALC: 176, 8 ± 12.1; TBC: 152.6 ± 8.9; ALTB: 201.6 ± 8.1, $P < 0.001$, central crossing: CTR: 10.9 ± 1.8; ALC: 25.0 ± 1.8; TBC: 18.5 ± 1.7; ALTB: 21.3 ± 1.3, $P < 0.001$). However, the total crossing was significantly higher in the group than in ALTB TAB group ($P < 0.001$). Frequency of rearing increased in the TBC group ($P < 0.001$) and the time of rearing decreased in ALC and ALTB groups ($P < 0.001$). Association ALTB increased the frequency and time of grooming ($P < 0.001$). Interestingly, IL-1□ and TNF-□ decreased in the frontal cortex of TBC and ALTB rats. In the hippocampus, IL-1□ decreased in the TBC group and TNF-□ increased in ALTB group compared with CTR group ($P < 0.05$). There was no difference in IL-10 or in other interleukin in the striatum of rats. **Conclusion:** Under our experimental conditions, combined exposure to alcohol and tobacco showed preponderance to psychostimulant effect, evidenced by the increase in total crossing and grooming behaviors. Combined use of alcohol and tobacco potentiates TNF-□ pro-inflammatory response in the hippocampus, indicating that this brain area is more susceptible to neuroinflammatory damage by association between alcohol and tobacco. **Financial support:** CNPq, CAPES, Propesq-UFRGS (CEUA-UFRGS, # 29773)

03.003 Fluoxetine prevents stress-induced alterations on behavioral, physiological and molecular parameters in Zebrafish. Marcon M[1], Mocelin R[1], Herrmann AP[2], Rambo CL[3], Koakoski G[4], Abreu MS[4], Conterato GM[5], Kist LW[3], Bogo MR[3], Zanatta L[6], Barcellos LJG[7], Piato AL[8] [1]UFRGS – Neurociências, [2]UFFS, [3]PUCRS – Biologia Celular e Molecular, [4]UFSM – Farmacologia, [5]UFSC, [6]UNOCHAPECO – Ciências Ambientais, [7]UPF – Bioexperimentação, [8]UFRGS – Farmacologia e Terapêutica

Introduction: The impact of stress in biological systems has been studied in several model organisms. Different protocols of unpredictable chronic stress (UCS) were established in rodents, however these protocols are expensive, long-lasting and require a large physical structure, besides presenting reproducibility difficulties among laboratories. The use of zebrafish (Danio rerio) as a model organism for stress studies shows various advantages in relation to other model organisms, such as low cost, easy maintenance and handling, and high genetic homology compared to the human species. The aim of this study was to evaluate the effects fluoxetineon behavioral, biochemical (whole-body cortisol), and molecular parameters (COX-2, TNF-α, IL-6 and IL-10) in zebrafish subjected to UCS for 7 days. **Methods:** The animals were divided into control and UCS groups. Within each group, the animals were further divided into control (without treatment) or fluoxetine (0.01 mg/L, in the home tank for 7 days and changed daily). Fish were submitted twice a day to one of the following stressors either during 7 days: heating tank water, social isolation, cooling tank water, crowding, low water level on housing tanks until animals dorsal body wall were exposed, tank change and chasing animals for 8 min with a net. To prevent habituation and maintain unpredictability, time and sequence of stressors presentation were changed daily. 24h after the last stressor, the animals were subjected to behavioral assessment (novel tank test) and the biological material collected for biochemical and molecular analysis. The data were evaluated by two-way ANOVA followed by SNK post-hoc test. **Results:** We replicated previous data showing that UCS induces behavioral and neuroendocrine alterations in zebrafish, and we showed for the first time that fluoxetine is able to prevent such effects. Furthermore, we extended the molecular characterization of the model, which revealed that UCS induced gene expression changes in the pro-inflammatory markers COX-2 and IL-6, which was also prevented by this antidepressant. **Conclusions:** This work showed that fluoxetine was able to prevent the effects caused by the UCS. The zebrafish is apromising model organism for studying the neurobiological basis of stress. Due to the translational relevance, the UCS can serve as a tool in the investigation of new drugs which can be used to treat stress. **Financial Support**: CNPq (472715/2012-7). **Approval by the ethics committee in the use of animals:** The protocol was approved by CEUA-UFRGS (# 27614).

03.004 The saccharin presence changes the value of cocaine on conditioning place preference but not for rats created in an enriched environment Freese L[1], Almeida FB[1], Heidrich N[2], Zavarize L[2], Fernandes P[2], Fonseca AR[3], Gomez R[4], Barros HM[1] [1]UFCSPA – Farmacologia, [2]UNISINOS, [3]UFRGS, [4]UFRGS – Farmacologia

Introduction: environmental enrichment (EE) may mimic positive life experiences and prevent the development of drug addiction. Conditioning Place Preference (CPP) indirectly measures the drug rewarding and reinforcing and enables the exploration of motivation pathways for the preference that occurs after conditioning paired with cocaine or other reward, as saccharin. Our objective was to verify if EE and the possibility of choosing between saccharin vs. cocaine changes the behavior of rats on cocaine CPP. **Methods**: Fifty male Wistar (21 PND) were raised in standard environment (ST) or in EE groups until adulthood (~ 350g). The EE wards hold 7 to10 rats in a large cage (70×60×80cm) divided in 3 floors connected by two ladders, with five/six toys replaced weekly and cardboard tunnels. The ST wards hold 2-3 rats in a standard polycarbonate cage (40×33×18 cm). The CPP boxes (40×60×38cm) had three distinct chambers equipped with photobeams. There were two larger conditioning chambers (40×23×38cm) connected by a central smaller neutral chamber (40×14×38cm) separated by doors containing distinct visual (vertical or horizontal lines/walls) and tactile (bars or leaked aluminum plate/floor) characteristics. The procedure started with experiment 1 (*cocaine vs. saline*): 1)*Pre-conditioning*: rats were placed in the neutral chamber and allowed free access (open doors) to all three chambers (15min). 2)*Conditioning*: over the next 8 days, rats underwent a daily 30 min conditioning session in which they were injected on alternate days with either saline (1mL/kg; i.p.) or cocaine (15mg/kg; i.p.) and confined to the respective paired chamber. 3) *Post-conditioning*: identical to the pre-conditioning test allowed the measure the time spent in the cocaine-paired chamber. For the experiment 2 (*saccharin vs. cocaine*) we observed the same stages above, but a saccharin solution [0,2%] was offered in place of saline. Statistical analysis: ANOVA 2V/Tukey. Ethics Council CEUA= 224/13. **Results**: On the experiment 1, the rats living in standard wards presented 2 times longer stay in the cocaine paired chamber than their own preconditioning side (P=0,027). In the experiment 2, we did not found differences. Thus, the presence of saccharin changes the conditioning cocaine behavior on the ST rats. We believe that is possible to better respond to the many questions we have regarding drug addiction using an animal models that's consider as well their lifestyle as for his choices. Prospects: Analyze the mRNA of BDNF levels, by Real-Time qPCR, to verify the BDNFs potential expression on prefrontal cortex and the hippocampus regions on the ST and EE groups.

03.005 TRKB-dependent antidepressant-like effect of losartan. Diniz CRAF[1], Casarotto PC[2], Castrén E[2], Joca SRL[3] [1]FMRP-USP – Farmacologia, [2]University of helsink, Finland – Neuroscience Center, [3]FCFRP-USP – Física e Química

Introduction: Pieces of evidence suggests that drugs blocking the angiotensin II (AngII) signaling could relieve depressive symptoms. Besides that, BDNF/TRKB expression is modulated with systemic AngII signaling blockade. BDNF, a neurotrophic factor acting on TRKB receptor, is involved in neuroplasticity, and antidepressant drug effects depend on BDNF/TRKB integrity. Despite this evidence, little is known about if antidepressant-like effect of compounds that interfere in angiotensin system depend on BDNF/TRKB signaling. Therefore, the aim of this study was to evaluate if supposed antidepressant-like effect of angiotensin-converting enzyme inhibitors (ACEi) or AT1 antagonist could be blockade with intracerebral infusion of k252 (functional TRKB blocker). Interaction between AngII and BDNF/TRKB signaling was also intended to be observed in rat-cultured brain. **Methods:** Male wistar rats were used to behavioral protocols as the forced swimming test (FST) or open field test (OFT). Stereotaxic surgery was performed to bilateral guide cannula placement in the dorsal hippocampus (DH), ventral hippocampus (VH) or in the medial prefrontal cortex (mPFC). Cultured cells from cortex or hippocampus of E18 rat embryos were used for *in vitro* experiments (western blotting or ELISA). **Results:** Losartan (LOS, 10mg/kg) decreased the immobility time on FST ($F_{3,25}$ = 3.74), without any effect on locomotion, but not captopril ($F_{4,15}$=0.43) or enalapril ($F_{3,28}$=0.36). LOS at 0.1, 1 and 10 nmol/side into VH was able to mimic i.p LOS effect ($F_{3,11}$ = 10.66), as did LOS 10nmol into mPFC (t_{12}=2.22), but not into DH ($F_{3,24}$ = 0.50). K252a infused into VH ($F_{3,15}$=5.36) or mPFC ($F_{3,13}$=4) was able to prevent losartan systemic effect. AngII increased TRKB phosphorylation levels on 816 tyrosine residue (pTrkB.Y816), while PD123319 (PD, AT2 antagonist) and k252, but not LOS, prevented that effect ($F_{3,28}$=6.77) in cultured cortical cells. TRKB.Fc (a BDNF scavenger) was not able to prevent AngII effect on pTRKB.Y816 ($F_{1,20}$=0.821). Curiously, PD prevented BDNF effect on pTRKB.Y816 levels ($F_{1,20}$=36.18), but not NGF effect on pTRKA.Y785 levels ($F_{1,13}$=0.60). PD was also able to block both BDNF ($F_{1,20}$=6.74) and AngII ($F_{1,19}$=5.08) effect to increase the coupling between TRKB:FYN (a member of the Src family). PD decreased, while AngII increased ($F_{2,30}$=24.33) Trk levels on cell surface. On cultured hippocampus, LOS *per se* increased pTRKB.Y816 levels and PD prevented the increase of pTRKB.Y816 levels from AngII ($F_{2,18}$=12.25). PP1 (a Src family kinase inhibitor) prevented AngII effect of increasing pTRKB.Y816 levels ($F_{1,20}$=6.17). Besides all, GFP-tagged AT2 and TrkB receptor were co-precipitated in cell lineage of fibroblast overexpressing TRKB receptors. **Conclusion:** It is suggested that AT1 antagonists could activate TRKB receptors by favoring AngII signaling through AT2 receptors, which could be coupled to TRKB as a heterodimer. BDNF-independent activation of TRKB by such mechanism seems to involve protein kinase FYN. Therefore, BDNF-independent TRKB transactivation could be relevant to the antidepressant effect of AT1 antagonists. **Financial support:** FAPESP and CNPq. **Local ethical committee:** experimental protocol 09.1.441.53.8

03.027 Activation of CB2 receptors mediates inhibitory effect of rimonabant in the cocaine responses: role of 2-arachinonoylglycerol. Gobira PH, Oliveira A, Gomes JA, Batista EM, Silva FR, Okine BN, Ribeiro FM, Finn DP, Aguiar DC, Moreira FA UFMG

Introduction: Stressful conditions are known to enhance animal's response to drugs of abuse, while environmental enrichment (EE) has been hypothesized to prevent and reverse behaviors underlying drug addiction. We have previously shown a protective effect of EE on ethanol sensitization and alcohol consumption; however the mechanisms underlying the protective effect of EE on ethanol-related behaviors need further investigation. **Methods**: Male Swiss mice were distributed in control (reared in standard cages), EE (kept in large cages with objects and a running wheel) and stress (ST) (kept in standard cages and exposed to restraint stress for 1 hour/day) groups, during 21 days. We first characterized the effects of the different rearing conditions on motor activity, novel object recognition, anxiety-like behavior and alcohol conditioned-place preference (CPP). Since oxytocin has a key role in social and stress responses, we also measured oxytocin receptor (OTR) binding in the brains of these mice, via autoradiography. Further, effects of EE on social reward and motivational state were studied using modified CPP and food enticing protocols, respectively. **Results**: We demonstrated that EE mice manifest lower locomotor activity and novel object exploration, suggesting a demoted motivational state. We also show an anxiogenic phenotype in the ST group, but not in the EE group. Although all mice showed ethanol CPP, EE group exhibited higher ethanol preference, suggesting a sensitization of the reward system and/or strengthening of associative memory induced by EE. When social and ethanol reward were confronted in the CPP, EE animals showed higher preference for ethanol, whereas controls had higher preference for social stimuli. These findings, in combination with the lower OTR binding in the prefrontal cortex and olfactory nuclei of EE mice, might indicate decreased social-induced reward due to the decreased numbers of OTR in sociability-related brain regions. On the other hand, social stimuli devaluated ethanol rewarding effects in controls, emphasizing the importance of the social aspect in drug dependence. In contrast, ST mice had higher OTR in the amygdala, plausibly associated with higher fear and anxiety. However, when motivation state was assessed (using palatable food), EE mice showed lower motivational behaviors than controls, despite their higher ethanol preference, indicating a differential effect of EE on different reward stimuli. Conclusion: We concluded that EE differentially alters brain systems underlying social *vs* drug-related rewarding processes and motivation. Supported by CAPES, CNPq, FAPESP and Santander. Animal Research Ethical Committee process number: 047, fls. 32, book 03.

03.007 Mechanisms involved in the cannabidiol antipsychotic profile. Pedrazzi JFC[1], Issy AC[2], Guimarães FS[3], Del Bel EA[2] [1]FMRP-USP – Neurociências, [2]FORP-USP – Fisiologia, [3]FMRP-USP – Farmacologia

Introduction: The information processing appears to be deficient in schizophrenia which is a highly disabling disease, and would involve an imbalance in the dopaminergic neurotransmission. Prepulse inhibition (PPI), measures the inhibition of a motor response by a weak sensory event is considered particularly useful to understand the biology of information processing in schizophrenia patients. Drugs that facilitate dopaminergic neurotransmission such as amphetamine (AMPH) induce PPI disruption in human and rodents. Clinical effective antipsychotics reverse the AMPH disruptive effect and can be considered predictive of antipsychotic action. Cannabidiol (CBD), a non-psychotomimetic constituent of the *Cannabis sativa* plant, has also been reported to have potential as an antipsychotic. Studies of our group demonstrated that CBD is able to attenuate the disruptive effect of AMPH in the PPI. CBD has been reported to act as an agonist of the vanilloid 1 channel in the transient receptor potential family (TRPV1) and also to inhibit the hydrolysis and cellular uptake of the endogenous cannabinoid anandamide (AEA). **Objective:** Our aim was to investigate in the PPI test the mechanisms enrolled in the CBD effects. **Methods:** To investigate the involvement of TRPV1 receptors in the CBD effects, male *Swiss* mice were systemically treated with either CBD or CBD preceded by the TRPV1 antagonist capsazepine (CPZ) prior to AMPH, and were exposed to PPI test. Since one possible mechanism of CBD action is the facilitation of endocannabinoid mediated neurotransmission through AEA, another group of mice received an AEA hydrolysis inhibitor (URB597) prior to the AMPH. Finally, we investigated if the application of CBD in the prefrontal cortex (PFC) would produce a similar effect of systemic CBD in the AMPH disruptive effect. The PPI test consist of 64 trials irregularly divided into pulse (P, white noise, 105dB), prepulse (PP; pure tone; 7kHz; 80, 85 or 90dB), prepulse + pulse (PP+P) and no-stimuli with white background noise level of 64dB – %PPI=[100-(PP+P/P)*100]. The percentage of PPI was analyzed with repeated measures with the treatment as the independent factor and the prepulse intensity as repeated measure. Duncan´s post hoc test ($p<0.05$) was used to specify differences. **Results:** Systemic CBD (30 or 60 mg/kg) attenuated the AMPH disruptive effects on PPI test at prepulse intensities of 80 and 85dB). CPZ blocked the ability of CBD (30 mg/kg) to reverse the AMPH effect at prepulse intensity of 85dB. The pretreatment with URB597 dose-dependently (0.3 mg/kg at all prepulse intensities and 1 mg/kg at 90dB) attenuated PPI impairment induced by AMPH. CBD (60 nmol) microinjected in the PFC attenuated the disruptive effect of AMPH (10 mg/kg) systemic treatment in the PPI response (85dB). **Conclusion:** CBD attenuates the AMPH disruptive effects in the PPI test, and this effect may be mediated by TRPV1 receptors as evidenced by the reversal of CBD effect by CPZ. In addition, we demonstrated that CBD microinjected in the PFC produces similar effects to systemic CBD treatment. Corroborating the hypothesis that AEA has a role in the CBD antipsychotic-like effects, we present, for the first time, that URB597 has similar effects to CBD in the PPI test. **Support**: FAPESP; CNPq; CAPES; NAPNA; USP.

03.008 Panicogenic-like effect induced by intra-PAG microinjection of ketamine. Silote GP[1], Oliveira SFS[2], Joca SRL[1], Beijamini V[2] [1]USP – Física e Química, [2]UFES – Ciências Farmacêuticas

Introduction: Ketamine, an dissociative anesthetic and non-competitive N-methyl-D-aspartate (NMDA) antagonist, induces rapid and relatively sustained antidepressant effect in pre-clinical and clinical studies (Machado-Vieira et al., 2009; White et al., 1982). However, the role of ketamine on anxiety remains uncertain. For example, Engin *et al.* (2009) showed that subanesthetic doses of ketamine induced anxiolytic-like effect in the elevated plus maze (EPM; Engin et al., 2009). In another study, subanesthetic doses of ketamine did not produce any effect in the EPM and light dark transition test (Carrier and Kabbaj, 2013). Furthermore, no study has investigated the effect of ketamine in panic disorder (PD). The periaqueductal gray matter (PAG) is a key structure in panic attack (Schenberg et al., 2001), The Elevated T-Maze (ETM) is an experimental model that allows the assessment of two behavioral correlates of anxiety in the same animal: learned anxiety (inhibitory avoidance), that seems clinically related to GAD; and innate fear (escape), related to PD (Zangrossi and Graeff, 1997). Then, we investigated whether intra-DPAG injection of ketamine would induce anxiolytic and/or panicolytic-like effects in animals exposed to the ETM. **Methods:** Adult male Wistar rats were submitted to stereotaxic surgery to insert unilaterally a stainless steel guide cannula (11,5 mm length) aimed at the DPAG (coordinates: AP: +1.6 mm from interaural at 15◦; L: 2.0 mm; 4.9 mm below the exterior surface of the skull). Five to seven days after surgery, intra-DPAG injections of ketamine (2 and 20 µg/0.2 µL) or saline were performed with a thin dental needle (12.5 mm long and 0.3 mm outside diameter) and, 20 minutes later, the rats were tested in the ETM. The ETM procedure consists in two tasks: the inhibitory avoidance (latency to the animal leave the enclosed arm) and escape (time to the animal leave one of the open arms), both performed in three trials. The locomotor activity of the animals was assessed in open field test immediately after the ETM test. **Results:** The repeated measure analysis of variance (ANOVA) showed that ketamine infused intra-DPAG did not change inhibitory avoidance. But the lowest dose of ketamine facilitated the escape 1 when compared with control group (saline: 13.14±3.86; ketamine 2µg: 5.0±0.53; ketamine 20 µg: 10.67±1.86; $F(2,22) = 3.531$, $p = 0.047$; Dunnett $p<0,05$), suggesting a panicogenic-like effect. Ketamine did not impair total traveled distance of rats in the open field when compared to the saline group. **Conclusion:** Intra-DPAG microinjection of ketamine induced a modest panicogenic-like effect. **Financial support:** CNPq e FAPES **UFES Animal Research Ethical Committee:** 048/2014 **References:** CARRIER, N. Neuroph, v. 70, p. 27, 2013. ENGIN, E. Neurosc**.**, v. 161, p. 359, 2009. MACHADO-VIEIRA, R. Pharmac & therap**,** v. 123, p. 143, 2009. SCHENBERG, L. C. Neuro Biobeh Rev, v. 25, p. 647, 2001. WHITE, P. F. Anesthes, v. 56, p. 119, 1982. ZANGROSSI, H. Brain res bull, v. 44, n. 1, p. 1, 1997.

03.009 Antidepressant-like effect induced by S-adenosyl-l-methionine. Sales AJ[1], Joca SRL[2] [1]FMRP-USP – Pharmacology, [2]FCFRP-USP – Physics and Chemistry

Introduction: DNA methylation, an epigenetic mechanism catalyzed by DNA methyltransferase (DNMT) enzymes and related to gene silencing, has been recently associated to the neurobiology of stress-related psychiatric disorders, such as depression. For instance, treatment with DNMT inhibitors induces antidepressant-like effects in preclinical rodent models. However, the effect of increasing DNA methylation induced by treatment with a methyl donor (S-adenosyl-l-methionine, SAM) treatment has been poorly investigated. Therefore, this work aimed a: 1) testing the effect induced by systemic treatment with SAM to mice submitted to the forced swimming test (FST), an animal model predicitive of antidepressant effects; 2) investigate the mechanisms involved in the behavioral effects induced by SAM. **Methods:** Male *Swiss* mice received systemic injections of imipramine (30mg.kg^{-1}), l-methionine (25, 50,100 and 200mg.kg^{-1}), SAM (25, 50 100 and 200mg.kg^{-1}) or vehicle. After 30 minutes, 7 or 14 days, the animals were submitted to the FST (6 minutes), when the immobility time was registered. One independent group was submitted to the same experimental protocol and sacrificed at time of testing (1 and 14 day) for collection of brain samples to further molecular analyses and no stressed group was used as control. DNA methylation was measured in the hippocampus (HPC) and prefrontal cortex (PFC). Additionally, male *Swiss* mice received systemic injections of the p-chlorophenylalanine (PCPA, serotonin synthesis inhibitor, 150mg.kg^{-1} daily) or vehicle for 4 days. 5 minutes after the last injection, the animals received injections of the SAM (50mg.kg^{-1}) or vehicle, and 30 minutes later, the animals were submitted to the FST. Furthermore, in order to investigate if treatments used could induce any significant exploratory/motor effect, which would interfere in the FST results, all animals were submitted to the open field test (OFT). **Results:** The administration of imipramine (30mg.kg^{-1}), l-methionine (25mg.kg^{-1}) and SAM (50mg.kg^{-1}) reduced the immobility time acutely, and this effect remained for 7 and 14 days after the treatment. In addition, stress reduced and l-methionine increased DNA methylation acutely in the CPF, but not 14 days later. However, SAM treatment did not attenuated stress-induced DNA methylation in none of the analyzed time. Yet, the PCPA pretreatment blocked the antidepressant-like effect induced by SAM. None of the treatments induced locomotor effects. The treatment effects were compared using one-way ANOVA followed by Dunnett's test for *post hoc* comparisons. Data from OFT were analyzed by a two-way ANOVA with the factors being treatment and injection. Probability less than 0.05 was accepted as significant. **Conclusion:** In conclusion, these results suggest that the antidepressant-like effect induced by SAM treatment might be a consequence of increased serotonin synthesis starting from SAM substrate. **Financial support:** CAPES, CNPq and FAPESP. **Process number:** 072/2014.

03.010 The PDE4-inhbitor roflumilast improves episodic memory: findings from a translational perspective Heckman PRA[1], Van Duinen MA[1], Vanmierlo T[1], Sambeth A[1], Ogrinc F[1], Tsai M[1], Lahu G[1], Uz T[1], Blokland A[1], Prickaerts J[1] [1]Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University, Maastricht, The Netherlands

Introduction: The cognition enhancing effects of the classic PDE-4 inhibitor (PDE4-I) rolipram have long been recognized. Considering the increasing need for cognition enhancers for treatment of several disorders, the translation to a human population seemed logical, but application of PDE-4Is was impeded due to emetic side effects. The development and approval of the PDE4-I roflumilast, which shows low emetic properties, allowed testing pro-cognitive PDE4-I cognition enhancing properties in humans for the first time **Methods**: We assessed the cognition enhancing potential of roflumilast in a translational setting, employing pre-clinical rodent studies as well as studies with healthy human volunteers. We specifically focused on the potential of roflumilast to improve memory in healthy adult mice (n=24; 7 months old), healthy young volunteers (n=20; 18-30 years old) and elderly (n=37; 60-80 years old) with normal memory function or more pronounced age-related impairment. **Results**: In mice, roflumilast improved memory consolidation in the Object Location Task at 0.03 mg/kg and had a modest effect in the spatial Y-maze at 0.1 mg/kg. Furthermore, both young and elderly healthy volunteers received single administration of roflumilast in a double-blind, placebo-controlled cross-over design using three doses (100 to 1000 µg range). Statistically significant improvements in Verbal Learning Task performance after single dose of roflumilast were observed in both subject populations with 100 mcg only. **Conclusion**: The current work shows that the second generation PDE4-I roflumilast significantly improved episodic memory in a translational setting. The next step in future studies would be chronic roflumilast treatment in clinical populations with memory impairment in order to demonstrate sustained treatment effect of roflumilast and to increase understanding of PDE4 inhibition on human cognitive function.

03.011 Antagonism of TRPV4 channel reduced depression-like behavior in mice. Alves VS[1], Dias FC[1,2], Matias DO[1,2], Cruz JVR[1], Miranda ALP[1,2,3], Figueiredo CP[1,2], Costa R[1,2] [1]UFRJ – Farmácia, [2]Ciências Farmacêuticas, [3]Farmacologia e Química Medicinal

Introduction: Depression is a common psychiatric disease that affects people's social life and their ability to work. The currently available antidepressant therapy is not entirely effective and it is associated with many side effects. Therefore, it is needed the search for new molecular targets and/or safe and effective drugs to control that disorder. Regarding the discovery of new molecular targets it is important to mention that transient receptor potential (TRP) channels are abundantly expressed in the brain, which might be relevant to psychiatric disorders. Indeed, it has been reported the antidepressant-like effect of agonists for TRP vanilloid-1 (TRPV1) channel member. Additionally, it was recently showed that TRPV4-deficient mice exhibit reduced depression-like and social behavior compared to wild-type mice. Thus, selective TRPV4 channel antagonists could be new therapeutic alternatives to treat depression. **Aim:** In this study we assessed the effect of selective TRPV4 antagonist (HC-067047) or agonist (GSK1016790A) on depressive-like behavior in the tail suspension test in mice. **Methods:** Male Swiss mice (25 – 30g, n = 8 per group) were treated with the selective TRPV4 antagonist (HC-067047 10 mg/Kg, s.c.) once a day for 6 days. In order to assess locomotor activity and depressive-like behavior, on the 7thday animals were submitted to open field and tail suspension tests, respectively. A different group of mice was injected with the selective TRPV4 agonist (GSK1016790A 0.3 nmol per site) by intracerebroventricular (i.c.v.) injection. After this, locomotor activity and depressive-like behavior were evaluated at 2 hours and 1, 3 and 7 days. **Results:** The repeated treatment with HC-067047 did not manifest significant changes in the mice's locomotor activity when compared to vehicle-treated animals, as assessed in the open-field test ($p<0,05$; Student`s t-test). However, the administration of HC-067047 significantly decreased the immobility time in the tail suspension test in comparison to vehicle treatment ($p>0,05$; Student`s t-test). Interestingly, the single injection of the selective TRPV4 agonist GSK1016790A did not cause significant alteration in the performance of mice in both open-field or tail suspension tests. **Conclusions:** The present findings show that repeated treatment with HC-067047produced antidepressant- like effect in mice. Additional studies are in course to better understand the role of TRPV4 on emotional behavior in mice. **CEUA/UFRJ**: 054/14 ; **Financial Support**: FAPERJ, CNPq e CAPES **Key-words:** TRPV4, HC-067047, tail suspension test, depression.

03.012 Antinociceptive, anti-inflammatory and anxiolytic effects of a novel agonist of opioid receptor. Rezende B[1], Montes GC[1], Silva BNM[2], Silva BV[2], Sudo RT[1], Zapata-Sudo G[1]
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Aims: The aim of this work was to evaluate the pharmacological profile of the derivatives in the central nervous system and the possible mechanisms involved to their action. **Methods and Results:** The protocols were approved by the Animal Care and Use Committee at Universidade Federal do Rio de Janeiro (CEUA/UFRJ DFBCICB068). Male *Swiss* mice (25–35 g) were used to investigate the effect of derivatives in the pentobartbital-induced hypnosis (10 animals/group). Vehicle or derivates (100 µmol/kg i.p.) were administered 10 min before the injection of pentobarbital (i.v.). The duration of hypnosis induced by pentobarbital was increased from 30.0 ± 2.2 min (vehicle) to 114.6 ± 11.8 min in mice treated with the triazol named PILAB 8. Hypnosis was also induced by intravenous injection of PILAB 8 (100 µmol/kg) with duration of 260.0 ± 58.9 s and pretreatment with CTOP, an µ-opioid antagonist, reversed the sleep time to 10.6 ± 2.8 s. Sedation and the locomotor activity was evaluated using the open field and rota rod devices, respectively. No sedation was observed in mice treated with PILAB 8 in a dose of 25 µmol/kg i.p. but in contrast, it was observed an anxiolytic effect evaluated in the elevate plus maze apparatus. PILAB 8 (25 µmol/kg i.p.) and midazolam (2 mg/kg i.p.) increased from 32.0 ± 4.0 to 64.0 ± 11.0 and 65.0 ± 7.0% the entry in the open arms, respectively, and decreased from 66.0 ± 5.0 to 35.0 ± 11.0 and 34.0 ± 7.0% the entry in the closed arms, respectively. Time in open arms was increased from 41.3 ± 6.0 to 161.0 ± 26.0 and 129.0 ± 35.0, respectively. The anxiolytic activity of PILAB 8 was reversed after treatment with naloxone, an opioid non-specific antagonist. Antinociceptive effect was also evaluated using the hot plate test and formalin-induced nociceptive behavior. PILAB 8 (25 µmol/kg i.p) exhibited antinociceptive activity (38.0 ± 8.0%) in the hot plate test. Administration of PILAB 8 and morphine reduced the reactivity induced by formalin from 44.0 ± 6.0 s to 21.0 ± 5.0 and 8.0 ± 4.0 s, respectively in the neurogenic phase. In the inflammatory phase, reactivity was decreased from 231.0 ± 54.0 s (vehicle) to 40.0 ± 17.0, 10.0 ± 6.0 and 136.0 ± 6.0 s after treatment with PILAB 8, morphine and acetyl salicylic acid, respectively. **Conclusions:** Antinociceptive and anti-inflammatory effects induced by PILAB 8 through the activation of µ-opioid receptors could be useful to treat cognitive disorders associated with pain. **Financial Support:** CNPq, FAPERJ, CAPES, INCT, PRONEX. **Keywords**: PILAB 8, opioid agonist, antinociceptive effect, anti-inflammatory action, anxiolytic, mice

03.013 Determination of the antioxidant potential of medicines used on the treatment of bipolar disorder and tobacco use disorder. Michelin AP[1], Bonifácio KL[1], Semeão LO[1], Farias CC[1], Higachi L[1], Matsumoto AK[1], Barbosa DS[2] [1]UEL, [2]UEL – Análises Clínicas e Toxicológicas

Introduction: The oxidative stress (OS) is defined as an imbalance between oxidant and antioxidant agents and these processes may result in toxic effects on cells and tissues by increasing the oxidation of lipids, proteins, carbohydrates, and DNA. The central nervous system is particularly vulnerable to OS, due to its elevated oxygen consumption and generation of free-radicals. A crescent series of evidences have demonstrated that the OS plays an important part in the bipolar disorder (BD) pathophysiology and in the disorder by the tobacco use disorder (TUD). The aim of this study was to evaluate if the drugs commonly used on the treatment of these pathologies present antioxidant effect to identify any other action mechanism beyond those already known. **Methods:** The antioxidant potential in vitro was evaluated for the drugs valproic acid (Depakene®), lithium carbonate (Carbolitium®), bupropion chlorhydrate (Bup®) and the manipulated formulation de n-acetil-cisteine (NAC) by colorimetric techniques 2,2-diphenyl-1-picryl hidrazila ($DPPH^{\bullet}$) and 2,2'azino-bis (3-ethylbenzthiazoline-6-sulphonic acid – $ABTS^{+}$). The reduction of the DPPH radical was based in its capability of reacting with hydrogen donating substances. In the presence of antioxidants, it receives H^{+}, therefore being reduced. The $ABTS^{+}$ technique monitors the decay of the cation-radical $ABTS^{\bullet+}$ by its removal when a sample containing substances with antioxidant properties is added. Both methodologies were applied in triplicate and under protection from light. **Results:** In the $ABTS^{+}$ and $DPPH^{\bullet}$ assay, NAC and Bupropion presented scavenging activity in a concentration-dependent manner. In $DPPH^{\bullet}$ test, NAC resulted in a linearity of R^2 0,9716 between 2,21 to 8,85 µg/mL. Maximum activity was found to be 92,18% at the concentration of 8,85 µg/mL and IC 50 was 4,28 µg/mL. While Bupropion resulted in a linearity of R^2 0,9711 between 6,63 to 66,33 µg/mL. Maximum activity was found to be 57,00 % at the concentration of 66,33 µg/mL and IC 50 of 49,48 µg/mL. In the $ABTS^{+}$ assay, NAC resulted in a linearity of R^2 0,9444 between 0,593 to 2,55 µg/mL. Maximum activity was found to be 76,07% at the concentration of 2,55 µg/mL and IC 50 of 1,11 µg/mL, whereas the Bupropion resulted in a linearity of R^2 0,9646 between 2,07 to 27,68 µg/mL. Maximum activity was found to be 66,46% at the concentration of 27,68 µg/mL and IC 50 of 13,94 µg/mL . On the other hand, the Valproic Acid and the Lithium did not present antioxidant activity in the colorimetric methodologies of $DPPH^{\bullet}$ and $ABTS^{+}$. **Conclusion:** Both NAC and Bupropion demonstrated electron donation action, stabilizing the $ABTS^{\bullet+}$ radical, and also the capability of donating hydrogen atoms to the $DPPH^{\bullet}$ radical. Therefore, these drugs presented antioxidant capabilities. Special thanks to CNPq for the financial support. Process number: 1.177.978.

03.014 Antioxidant action of some antipsychotics in *in vitro* models. Semeão LO, Brinholi FF, Michelin AP, Matsumoto AK, Farias CC, Higachi L, Bonifácio KL, Barbosa DS UEL

Introduction: Schizophrenia (SCZ) is a chronic, severe and disabling psychiatric illness. Evidences suggest that excessive free radical production or oxidative stress may be involved in SCZ. Presently, pharmacological management of SCZ involves the use of one or more antipsychotics, which are classified as first-generation or typical such as haloperidol (HAL) and second-generation or atypical such as clozapine (CLZ), risperidone (RIS), olanzapine (OLZ), quetiapine (QTP) and ziprasidone (ZPS). But, it remains controversial the impact that typical vs. atypical antipsychotics has on the oxidative stress status in SCZ patients. The main objective of this study were analyze, *in vitro*, the six antioxidant potential (CLO, HAL, RIS, OLZ, QTP and ZPS) used in treatment of SCZ. **Methods**: *In vitro,* the antioxidant capacity of six antipsychotics was assessed by their ability to: donate hydrogen and stabilize the free radical 2,2-diphenyl-1-picryl-hydrazyl ($DPPH^{?}$); and scavenge 2,2?-azino-di-(3-ethylbenzthiazoline-6-sulphonic acid ($ABTS^{+}$). The *in vitro* concentration of drugs that caused 50% of $DPPH^{?}$ and $ABTS^{+}$ scavenging was considered the mean inhibitory concentration (IC_{50}). The IC_{50} was determined by GraphPadPrism® software, version 3.02, using hyperbolic curve (one site binding hyperbole). Antioxidant activity results are presented as means ± standard error mean (SEM). **Results** were considered statistically significant if p**Results**: In the $ABTS^{+}$ and $DPPH^{?}$ assay, CLZ, OLZ and ZPS presented scavenging activity in a concentration-dependent manner. In $ABTS^{+}$ assay, CLZ resulted in a linearity of R^2 0.9955 between 0.00 to 0.005mg/mL. Maximum activity was found to be 98.5% at the concentration of 0.00498 mg/mL and IC_{50} was 0.0012mg/mL. OLZ resulted in a linearity of R^2 0.9843 between 0.00 to 0.04mg/mL. Maximum activity was found to be 96.3% at the concentration of 0.0396 mg/mL and IC_{50} was 0.001 mg/mL. ZPS resulted in a linearity of R^2 0.9976 between 0.00 to 0.16 mg/mL. Maximum activity was found to be 96.4% at the concentration of 0.159 mg/mL and IC_{50} was 0.0105mg/mL. In $DPPH^{?}$ test, CLZ resulted in a linearity of R^2 0.9958 between 0.00 to 0.008 mg/mL. Maximum activity was found to be 86.2% at the concentration of 0.00747 mg/mL and IC_{50} was 0.003mg/mL. OLZ resulted in a linearity of R^2 0.9875 between 0.00 to 0.08 mg/mL. Maximum activity was found to be 95.6% at the concentration of 0.0787 mg/mL and IC_{50} was 0.003mg/mL. ZPS resulted in a linearity of R^2 0.9955 between 0.00 to 1.0 mg/mL. Maximum activity was found to be 98.6% at the concentration of 0.948 mg/mL and IC_{50} was 0.044 mg/mL. HAL QTP and RIS did not present scavenging activity and the concentration-response curve parameters could not be calculated. RIS, HAL and QTP lacked antioxidant effects. **Conclusion**: Summing up, our study shows *in vitro* antioxidant properties of some atypical antipsychotic drugs, especially CLZ, OLZ and ZPS which may result in improved clinical outcomes in SCZ, a disease in which oxidative stress may play a key role. This antioxidant capacity suggests that these drugs may have a neuroprotective mechanism on the top of their antipsychotic mechanism of action. Thanks to Fundação Araucária for the financial support.

03.015 Purinergic receptors are involved in processing contextual fear conditional responses in rodents. Domingos LB[1], Hott SC[2], Resstel LBM[1] [1]USP – Pharmacology, [2]UFES – Pharmaceutical Sciences

Introduction: The purinergic system comprehends two large receptor families-P2X and P2Y. Both receptors are activated by adenosine triphosphate (ATP), although they present different functions (Abbracchio and Burnstock, Pharmacol Ther, 64:445,1994).These receptors are present in several brain regions, involved in the control of emotion and behavioral responses. Therefore, it is suggested their participation in fear- and anxiety-related responses. However, few studies investigate the role of purinergic system on threatening situations, such as those observed on contextual fear conditioning (CFC). In this animal model, an aversive unconditioned stimulus (US), as a foot-shock, is paired with a neutral conditioned stimulus (CS), such as a context/chamber. CFC is evoked when re-exposing the animal to the CS, without US presentation, generating conditioning emotion responses (CER). CER is composed by autonomic changes and freezing behavior, which is characterized by the lack of movement, except for those necessary for breathing(LeDoux JE,Annu Rev Neurosci 23:155,2000). Moreover, repeated exposure to the CS without US presentation promotes extinction of the aversive memory. Interestingly, CFC is associated with behavior therapy in humans associated with treatment of several psychiatric disorders, such as posttraumatic stress disorder (PTSD). **Objective:** Considering the above mentioned, we aimed to investigate the participation of purinergic receptors P2XR on the expression and extinction of aversive memories. **Methods:** Male mice (8-10 weeks) were used. P2X7 Knockout (P2X7 KO) mice (C57BL/6 background) and wildtype (WT) mice were submitted to contextual conditioning session for 5 min (three footshocks;0.85mA;2sec duration). Twenty-four hours after training, mice were re-exposed to the training context during 21min for the extinction session. Again, after another 24h, animals were re-submitted to the contextual chamber during 5 min for the test session. The experiments were design in two separate groups. 1) WT mice received intraperitoneally (10 ml/kg,10 min before test session) either P178, a nonselective P2R antagonist (10 mg/kg and 30 mg/kg;n=6-7); A438079, a selective P2X7 antagonist (10mg/kg;n=6), MRS2179, a selective P2Y1 antagonist (10mg/kg; n=5), or vehicle (saline;ip;n=7). 2) P2X7 KO and their WT control were submitted to the CFC protocol. **Results:** As results, we observed increased contextual fear expression ($F_{2,17}$=5.5,P<0.05) and impaired acquisition of extinction ($F_{2,17}$=6.2,P<0.01) after treatment with the higher dose of the nonselective P2R antagonist. Similar results were observed with the selective P2X7 antagonist, A438079 ($F_{2,98}$=29.6,P<0.05), but not after treatment with the selective P2Y1 antagonist MRS2179 (P>0.05). Additionally, P2X7 KO mice showed increased contextual fear expression (t_{16}=2.84,P<0.05) and impaired acquisition of extinction ($F_{1,105}$=25.5,P<0.01) compared to mice WT, corroborating the data obtained by pharmacologic P2X7 antagonism. **Conclusion:** We suggest that the pharmacological or genetic blockade P2X7 receptors promote anxiogenic-like effects and impairment in aversive extinction learning processes in the CFC protocol. Therefore, the activation of these receptors presents an alternative for treatment of psychiatric disorders. **Financial support:** FAPESP, FAEPA, CAPES, CNPq. Ethical Committee approval (Process no. 043/2013)

03.016 Effect of copaiba oil on alcohol voluntary intake in rats. Pulcinelli RR, Bandiera S, Santos P, Giustina CD, Gomez R UFRGS – Farmacologia e Terapêutica

Introduction: Copaiba resin oil (CO) has been widely used in folk medicine for multiples diseases, especially as an anti-inflammatory. It is rich in sesquiterpenes, as β-caryophyllene, a substance that reduces alcohol voluntary intake in mice after intraperitoneal administration. The aim of this study was to evaluate the effects of CO on alcohol voluntary intake in rats after subcutaneous administration. **Methods:** Male Wistar rats (270-280 g) were treated with 2 g/kg alcohol (ALC: 20% w/v, n = 20) or tap water (CTR; n = 20) by oral gavage, twice daily, for 6 days, to induce dependence. In the next 4 weeks, rats were free to choose from a bottle containing saccharin solution 0.2% or another one containing alcohol (20% w/v) with saccharin 0.2%. CTR group was allowed to choose between 2 bottles containing saccharin 0.2%. The daily liquid consumption of both groups was monitored. On the day 16 of self-administration they were divided into 4 groups which received 600 mg/kg CO (CTR-CO and ALC-CO groups), diluted in sunflower oil, subcutaneously, once a day, for 3 days, or sunflower oil (CTR and ALC groups). **Results:** Total volume of liquid consumed per week was twice higher in the ALC than CTR group ($P < 0.001$), with no effect of CO treatment. However, CO reduced alcohol intake 2, 3 and 6 days after the last administration ($P = 0.034$), suggesting an anti-addictive effect of CO. Six days after the last administration there was also a reduction in preference for alcohol in ALC-OC group ($P = 0.050$). **Conclusion:** Copaiba oil, administered subcutaneously, reduced the voluntary alcohol consumption in rats a few days after administration, observed by lower preference and quantity ingested of alcohol compared to non-treated rats. These data suggest the potential anti-addictive of copaiba oil. Further studies are necessary to determine the mechanisms involved in this effect and explore the effects of oral administration.
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03.017 Acute effect of L-Arginine on general activity observed in the open-field arena and its dyskinetics movements after haloperidol acute treatment in rats. Mariani MP[1], Gemignani S[2], Pedroso-Mariani SR[2] [1]PUC-Campinas- Farmacologia, [2]FMJ – Farmacologia

Introduction: The L-arginine coming from diet and is the precursor of the nitric oxide(NO). The NO is a radical that can also act as an atypical neurotransmitter and influences dopamine-mediated neurotransmission (Curr Pharm Des. 17(5):471-88, 2011). This pathway (L-arginine-NOS-NO-cGMP) has a role in modulating central nervous system mechanisms in motor behavior, anxiety and stress. The aim of this work was to study the action of acute administration of Arginine (Arg) after acute haloperidol pre-treatment (Halo) on the general activity observed in rats in the open-field arena on frequency of locomotion (FL) and the effects on jaw movements (JM) and protrusion of the tongue (PT). **Methods:** (EAEC-FMJ number: 165/09) male Wistar Rats (N= 20), weighing 280 g on average, were divided into 4 groups. The animals in the control group (C) were injected with saline (1ml/kg, i.p.), the Halo group treated with haloperidol (3mg/Kg, i.p.) and the Arg group was injected whith Arginine (120mg/Kg, i.p.). The fourth group (Halo+Arg) was Halo twenty minutes before the administration of Arg (in the same doses for the individual groups mentioned). After twenty minutes it was recorded the activity of these animals in the open-field arena, during 5 minutes (frequency of locomotion).Then, the animals were isolated in metal cages for observation for ten minutes and the frequencies of JM and PT were recorded (Neiswander,J.L. et al. , Psycopharmacol,116:79,1994). These equipments are suitable for the evaluation of substances that act on the central nervous system, in particular in nucleus acumbens (voluntary movement) and striatus (involuntary movements, balance, dopaminergic/cholinergic, dyskinesias) (WOLF, M.E. et al. Biol.Psycoat.,18:1181, 1983). **Results:** Data are presented as mean ± standard deviation and have been analyzed by ANOVA. The frequency of JM in rats with Halo treatment (33.40 ± 9.79) had significant increase when compared to the control animals (6.80 ± 2.28) ($p<0.05$ Tukey-Kramer Test). However, in animals administered with Arg (9.80 ± 3.42) and Arg + Halo (7.8 ± 1.30) group presented JM similar to control. The Frequency of Locomotion (FL) in the open-field arena obtained using Halo (2.20 ± 1.10) and Arg (6.60 ± 3.85) presented significant decrease when compared to the control (28.80 ± 11.69). The Arg + Halo group has a cataleptic effect. **Discussion:** The Arginine has not changed JM in dose studied. However, the interaction between Halo and Arg reversed the Haloperidol effect. One possible explanation for these results is related to changes in the expression of NOS activity or percentage of D2 receptor occupancy, with this change was not induced dyskinesia. It provides evidence of a protective role of Arginine on neurodegenerative processes in the nigrostriatal pathway. The results of the frequency of locomotion for the group (Arg + Halo) indicate that the changes were not modify the decrease in motor activity haloperidol-induced. Our results indicate that Arginine may be a promising therapeutic target for reduction of neuroleptics-induced dyskinesia. **Financial Support:** FMJ, PUCC.

03.018 Effect of a Nociceptin/Orphanin FQ receptor agonist on aggressive behavior in male mice. Silva EF[1], Silva AI[1], Souza LS[1], Santos WB[1], Guerrini R[2], Asth L[1], Calo' G[3], Gavioli EC[1] [1]UFRN – Biofísica e Farmacologia, [2]University of Ferrara – Chemical and Pharmaceutical Sciences and LTTA, [3]University of Ferrara – Medical Science, Section of Pharmacology and National Institute of Neuroscience

Introduction: Aggression is a behavior shown by several species including humans, and violence and impulsivity related to aggressiveness represent a social problem. Indeed, they can be considered symptoms of many psychiatric disorders. Some of the brain areas related to aggressiveness include amygdala, hypothalamus, and prefrontal cortex. Besides, aggressiveness is mediated by different neurotransmitters, such as serotonin, dopamine, noradrenaline, and GABA that are the available therapeutic targets to treat aggressiveness. Nociceptin/orphanin FQ (N/OFQ) is a heptadecapeptide acting as endogenous ligand of the NOP receptor. Clinical and preclinical findings suggest the involvement of N/OFQ – NOP receptor system in psychiatric disorders, including those related to aggressiveness.
AIM: This study investigated the effects of standard drugs and the NOP receptor agonist Ro 65-6570 on aggressiveness in mice submitted to the resident-intruder test. **Methods**: Male Swiss mice were used. Valproate 300 mg/kg, Lithium 50 mg/kg, and Carbamazepine 20 mg/kg were used as standard drugs. Ro 65-6570 was tested in the 0.01, 0.03, 0.1 and 1 mg/kg range of doses. In the resident-intruder test, male mice were housed individually for 7 days (residents) before the experiment. The aggressiveness of each resident mouse was tested twice by inserting an intruder mouse in the resident cage for 10 min. At 8th day of experiment, the resident was tested with no treatment and its basal aggressiveness was recorded; at 11th day, the same mouse was re-tested after being treated. All drugs were injected ip in the resident mouse 30 min before the test. Open field was used to evaluated locomotor activity of mice.
Results: Valproate, Lithium, and Carbamazepine reduced the aggressiveness in resident-intruder test. Mice treat with Valproate showed a tendency to hyperlocomotion. Lithium and Carbamazepine did not change locomotor activity. Ro 65-6560 at all doses tested increased aggressiveness, but it did not change locomotor activity. **Conclusion**: Standard mood stabilizers are able to decrease aggressiveness in mice subjected to resident-intruder test. In addition, this study suggests the involvement of nociceptin/orphanin FQ – NOP receptor system on the modulation of aggressive behavior. **Financial Support**: CNPq and CAPES. RESEARCH APPROVAL: This study was approved by Animal Research Ethical Committee (CEUA/UFRN). Protocol number: 041/2014.

03.019 Psychopharmacological effects of N-Acetylcysteine. Benvenutti R, Santos P, Giongo FK, Fortes LS, Hermann AP, Elisabetsky E UFRGS

Introduction: Anxiety disorders are chronic and may be incapacitating, with an estimated prevalence of about 25 to 30% of the population. The drugs available for treating these disorders have many adverse effects and are often less effective than expected. Furthermore, a significant fraction of patients (20-47%) are refractory to available treatments. Therefore, it is relevant to develop new drugs with innovative mechanisms of action, higher efficacy and fewer adverse effects. The glutamatergic system has been considered as a target for treating psychiatric disorders. N-acetylcysteine (NAC) is a glutamatergic modulator that has shown positive effects in both pre-clinical models and clinical trials of various psychiatric disorders, including depression and schizophrenia. However, little is known regarding the effects of NAC the context of anxiety disorders. Thus, the present work aimed to verify the effects of NAC on animal models of anxiety. **Methods**: Male CF1 adult mice and BALB/C mice were used to verify NAC effects on the Stress-Induced Hyperthermia (SIH) and Elevated T-maze (ETM) tests, respectively. Saline, NAC (60 or 100 mg/kg) or diazepam (1 mg/kg) were intraperitoneally (i.p.) administered 1 hour before tests in acute experiments, while in sub-acute experiments 4 consecutive daily i.p. injections were administered (the last injection was performed 1 hour before tests). In SHI test body temperature is measured twice, where the first measurement of rectal temperature (T1) induces a mild stress that causes an increase in temperature, which can be seen after 15 minutes in the second measurement (T2). Thus, the stress-induced hyperthermia is determined by the difference between T2 and T1. The ETM is a T-shaped apparatus with three arms of identical dimensions, elevated 50 cm from the floor, which has one arm enclosed by Plexiglas walls perpendicular to two opposed open arms. The time taken by the mouse to withdraw from the enclosed arm (inhibitory avoidance) was recorded in three consecutive trials of 300 s cut-off each, with 30 s interval between them. Drugs with anxiolytic profile are able to impair the inhibitory avoidance acquisition in ETM and prevent stress – induced hyperthermia. For ETM test animals were housed 4 per cage, for SIH the animals were kept 4 per cage and single - housed 24 hours before test. **Results**: Acute NAC was devoid of effects in SIH or ETM tests. On the other hand, sub-acute NAC (60 and 100 mg/kg) was able to prevent the temperature increase in the SIH test in CF1 mice. Regarding ETM, only sub-acute NAC treatment at the higher dose (100 mg/kg) impaired inhibitory avoidance acquisition of open arms in BALB/C mice, also indicating an anxiolytic effect. Conclusion: NAC sub-acute showed anxiolytic activity in the SIH and ETM models of anxiety. These data support the potential of NAC potential as an anxiolytic and serves subsidizes the necessary clinical trials. The effects of NAC in psychiatric disorders are probably due to its multifaceted mechanism of action, since it modulates glutamate and other neurotransmission systems and, in addition, it has antioxidant and anti-inflammatory activities. **Financial support**: CNPq.All protocols were approved by the Ethics Committee of the Institution (27553/2015).

03.020 Involvement of Nitrergic neurotransmission in the dorsolateral periaqueductal gray on rats escape-response expressed under hypoxia condition. Gripp-Fernandes G, Frias AT, Spiacci Junior A, Zangrossi Junior H FMRP-USP

Introduction: It has been proposed that hypoxia challenge is an effective stimulus to activate the suffocation alarm system and consequently evoke panic attack in both humans and rats[1,2]. Since nitric oxide (NO) plays an important role on defensive behaviors, here, we evaluated the effects promoted by systemic injection of nitric oxide synthase inhibitors on panic-like escape response elicited in rats exposed to hypoxia condition. Subsequently, we extended the analysis to the dorsolateral periaqueductal gray (dlPAG) based on evidence suggesting that this midbrain structure harbors a hypoxia-sensitive suffocation alarm system[3] and that nitrergic neurotransmission, in the dlPAG, play a modulatory role in the expression of escape behaviors[4]. **Methods**: male Wistar rats were treated for 7 days with aminoguanidine (15mg/kg) or acutely with 7-NI (15mg/kg), both NO synthase (NOS) inhibitors or Alprazolam (2mg/kg), a clinically effective panicolytic drug. Thirty minutes after the last injection the animals were submitted to hypoxia challenge. In the central analyses, animals were intra-dlPAG injected with a nitric oxide scavenger, carboxy-PTIO (c-PTIO, 0.3, 1 or 3 nmol/ 0.2µL), the selective inhibitor of neuronal nitric-oxide systhase (nNOS), n-propyl-l-arginine (NPLA) (0.004, 0.04 or 0.4 nmol / 0.2µL), or vehicle ten minutes before the hypoxia challenge. The test apparatus consists of a circular Plexiglas chamber (30 x 35 cm) sealed by a removable cap and connected to gas cylinders. Initially, the animal was placed into the chamber under normoxia condition (21% O_2, 78% N_2) and the locomotor activity was evaluated over 5 minutes. Subsequently, hypoxia (7% O_2, 92% N_2) was achieved in 240s by flushing 100% N2 (4.5 L/min) into the chamber and it was maintained over 360 min, when number of jumps were analyzed. **Results**: The systemic administration of NOS inhibitors aminoguanidine and 7-NI and of the high potency benzodiazepine alprazolam reduced the number of jumps elicited by hypoxia. Similar effect was observed with intra-dlPAG injection of c-PTIO and NPA. Conclusion: The results herein suggest the involvement of NO-mediated neurotransmission in the dlPAG in the genesis/regulation of panic-like defensive behaviors elicited by hypoxia. **Reference**: [1] Beck JG, Ohtake PJ, Shipherd JC. J Abnorm Psychol. 108(3):473, 1999. [2] Spiacci, et al. Neuroscience, 307: 191, 2015. [3] Schimitel, FG et al. Neuroscience. 200: 59 ,2012. [4] Fogaça, et al. Braz J Med Biol Res, 45 (4): 357, 2012. **Financial Support**: CNPq and CAPES. Animal Ethic Committee Number: 177/2015.

03.021 Antipsychotic-like effects of cannabidiol on social interaction and cognitive impairment induced by MK-801. Rodrigues NS[1], Silva NR[1], Gomes FV[2], Guimarães FS[1]
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Introduction: Cannabidiol (CBD), a non-psychotomimetic compound found in the Cannabis sativa, induces antipsychotic-like effects (Campos *al.,* 2012). Repeated administration of CBD prevented schizophrenia-like signs induced by chronic treatment (28 days) with MK-801, an NMDA receptor antagonist, when both drugs were administered concomitantly (Gomes *et al.,* 2015). Behavioral changes induced by NMDA antagonists have been observed up to 6 weeks after the end of the treatment and can be reversed by atypical but not by typical antipsychotics (Hashimoto *et al.*, 2005). In the present study, we evaluated whether a shorter repeated treatment period with MK-801 (7 or 14 days) would induce long-lasting deficits in the novel object recognition (NOR) and social interaction (SI) tests. We also tested if repeated CBD treatment after the end of the MK-801 treatment period would reverse these deficits. **Methods:** Male C57BL/6J mice received daily intraperitoneal injections of MK-801 (0.25, 0.5 or 1 mg/kg, twice a day) for 7 or 14 days. SI was performed 8 days after the end of the MK-801 treatment. Twenty-four hours later, animals were submitted to the NOR test. After that, we investigated if repeated treatment with CBD (15, 30 or 60 mg/kg; once a day for 7 days, i.p.) would reverse MK-801-induced changes. CBD treatment began 24h after the end of the MK-801 treatment. Forty-eight hours after the last injection animals were submitted to SI and, 1 day later, to the NOR test. CBD effects were compared to those induced by repeated clozapine (1mg/kg) treatment. **Results:** Behavioral impairments were observed only after the treatment with MK-801 (0.5 mg/kg) for 14 days, but not for 7 days. Repeated CBD or clozapine treatment reversed the impairment induced by MK-801 in both SI and NOR tests. **Conclusion:** These data reinforce the proposal that CBD has antipsychotic-like properties and indicate that CBD could be an interesting alternative for the treatment of the negative and cognitive symptoms of schizophrenia patients. **Financial support:** CAPES, CNPq and FAPESP. **Approval by the animal research ethical committee:** process number 145/2015 **References:** Campos, A. C. et al. Philos Trans R Soc Lond B Biol Sci, v.367, n. 1607,p. 3364–78, 2012. Gomes, F. V. et al. Schizophr Res. v.164, n.1-3, p.155-63, 2015. Hashimoto, K. et al. Eur J Pharmacol, v. 519, n. 1-2, p. 114-7, 2005.

03.022 Phentolamine microinjected into the dorsal periaqueductal gray matter attenuates anxiolytic-like effect of noradrenaline in rats tested in the elevated T-maze. Carvalho JJV[1,2], Souza DO[3], Beijamini V[1,3], Martins JM[1,2], de Bortoli VC[1,2,3] [1]UFES – Bioquímica e Farmacologia, [2]CEUNES/UFES – Ciências da Saúde, [3]UFES – Ciências Farmacêuticas

Introduction: Several studies have associated the dorsal periaqueductal gray matter (DPAG) with anxiety disorder. In the elevated T-maze (ETM), the pharmacological validation associated the inhibitory avoidance with generalized anxiety disorder and the escape behavior with panic disorder [1]. In a previous study we found that intra-DPAG administration of noradrenaline impaired the inhibitory avoidance in animals exposed to the ETM without changing escape behavior, suggesting only an anxiolytic-like effect. Therefore, the present study aimed to evaluate if alpha-adrenergic receptors mediate the anxiolytic-like effect of noradrenaline microinjected in the DPAG of rats tested in the elevated T-maze. **Methods**: Male Wistar rats (220-250 g) were microinjected in the DPAG with phentolamine (10 nmol/ 0.1 µL; a non-selective alpha-adrenoceptor antagonist) or saline 10 minutes before microinjection of noradrenaline (60 nmol/0.1 µL) or saline. Rats were submitted to the ETM 30 s after the last injection. After the ETM test, the animal was placed in the open field to measure locomotor activity for 5 minutes. To evaluate the avoidance and escape data in the ETM, a repeated measures analysis of variance (ANOVA) followed by Tukey post hoc was performed.The data from the open-field test were analyzed by one-way ANOVA followed by Tukey test when appropriated. The significance level was set at $p < 0.05$. **Results**: The results showed that the impairment of the inhibitory avoidance acquisition induced by noradrenaline in the ETM was attenuated by intra-DPAG injection of phentolamine [(mean ± SEM, seconds): saline/saline = 152.00 ± 33.51 (n= 10); saline/noradrenaline = 16.38 ± 2.27 (n= 8); phentolamine/saline = 113.25 ± 29.31 (n= 8); phentolamine/noradrenaline = 72.18 ± 24.49 (n= 11)]. There was no effect on the escape behavior in the ETM or on locomotor activity in the open field.
Conclusion: Our results suggest that the anxiolytic-like effect of noradrenaline injected in the DPAG is partially mediated by alpha-adrenergic receptors. **Reference**: [1] GRAEFF et al. Neurosci Biobehav Rev 23: 237, 1998. Financial Support: FAPES and CNPq (Process Number 53672313/11). Commission ethical protocol number 046/2014, CEUA-UFES.

03.023 SK3 channel overexpression decreases survival and neuronal fate in the dentate gyrus of adult mice. Scarante FF[1], Martin S[2], Lazzarini M[2], Prado LA[3], Stühmer W[2], Del Bel EA[4], Campos AC[1] [1]FMRP-USP – Farmacologia, [2]Max Planck Institute of Experimental Medicine – Molecular Biology of Neuronal Signals, [3]Max Planck Institute of Experimental Medicine – Oncophysiology Group, [4]FORP-USP – Morfologia, Fisiologia e Patologia

The small-conductance Ca^{2+}-activated K^+ channels type 3 (SK3) have been associated with the cognitive deficits found in schizophrenia. Moreover, its overexpression in mice induces shrinkage of the hippocampal formation and memory impairment. Nevertheless, the mechanisms associated with these behavioral and morphological alterations are still unclear. Therefore, considering that these channels constitute the main SK channels expressed in neural stem cells and that the dentate gyrus (DG) of the hippocampus is one of the main neurogenic niches found in the adult brain, the present study aimed to assess the involvement of SK3 channel in adult hippocampal neurogenesis. Male transgenic mice constitutively overexpressing SK3 (T/T; n=5) and their wild-type littermates (WT; n=5) were injected with bromodeoxyuridine (BrdU, 100mg/kg) for 2 consecutive days and, 17 days after the last BrdU administration, they were perfused under deep anesthesia, the brains removed and sliced (30um). Slices containing the hippocampal formation were processed on a free-floating immunofluorescence procedure, targeting BrdU, NeuN and doublecortin (DCX) labelling. Confocal microscopy analysis showed that the T/T mice presented a lower number of BrdU-positive cells than the WT littermates, although it did not reach statistical significance (values obtained after correction by the dentate gyrus size: WT: 48334721±7589190, T/T: 26078376±8236420; Independent-samples t test, p=0,082). The co-labelling of BrdU with NeuN or DCX/NeuN were also evaluated, but no statistical differences were detected. However, the percentage of BrdU/DCX-positive was 227% higher for the WT mice (Independent t test; p=0,053) when compared to T/T mice, indicating lower number of newly-generated neurons in the DG of T/T mice. These preliminary data indicate that the overexpression of SK3 might affect survival and neuronal fate commitment of newly generated cells in the hippocampus. However, further studies are needed to determinate the role of this channel in other steps of this process, as well as to assess what would be the contribution of defective adult neurogenesis on the behavioral outcomes of SK3 overexpression in mice. Financial Support: CNPq. Animal Research Ethics Committee Approval Number: AZ 33.9-42502-04-10/0314.

03.024 Intra-dorsal periaqueductal gray injection of noradrenaline induces anxiolytic-like effects in the light-dark transition test Souza DO[1], Carvalho JJV[2], Beijamini V[1,2], Martins JM[1,2], Bortoli VC[1,2] [1]UFES – Pharmaceutical Sciences, [2]UFES – Bioquímica e Farmacologia

Introduction: The role of the dorsal periaqueductal gray matter (DPAG) in fear and anxiety has been studied over the last decades. The evidence regarding the involvement of the noradrenergic system in anxiety is conflicting, depending on brain structure studied. Thus, in the present study we tested the hypothesis that noradrenaline injected directly in the DPAG of rats has anxiolytic-like effect in the light-dark transition test. The light-dark transition test is an ethological model of anxiety, quick and easy to perform, that does not require animal training. **Methods**: Male Wistar rats (220–250g) with guide-cannula aimed at the DPAG received microinjections of noradrenaline (30, 60 and 90 nmols) or saline and were tested on light-dark transition model 30 seconds later. Immediately after the light-dark transition test, the locomotor activity of animals was assessed by number of line crossings in the open field during 5 minutes. The parameters measured in the light-dark transition test were the latency time to the first entry in the dark compartment, the number of transitions and the time spent in the light compartment during 5 minutes. The data from light-dark and open field test were analyzed by one-way ANOVA followed by Tukey test when appropriated. The significance level was set at $p < 0.05$. **Results**: Noradrenaline (30 and 60 nmols) increased the percentage of time spent in the light compartment [(mean ± SEM): saline= 11.21 ± 5.42 (n=10); noradrenaline 30 nmols= 24.28 ± 3.4 (n=10); noradrenaline 60 nmols= 21.00 ± 2.7 (n=10)] and number of transitions between light and dark compartments [(mean ± SEM): saline= 4.91 ± 0.7; noradrenaline 30 nmols= 9.73 ± 1.14; noradrenaline 60 nmols= 8.2 ± 0.74]. There was not a significant treatment effect on the latency to the first entry in the dark compartment. Also, noradrenaline did not change locomotor activity in the open field compared to the control group. Conclusion: Our results indicate that noradrenaline infused in the DPAG induces an anxiolytic-like effect in the light-dark transition test. **Financial support**: FAPES Commission ethical protocol number 046/2014, CEUA-UFES.

03.025 Effect of nNOS inhibition in 5-HT1A receptor expression of the animals exposed to the learned helplessness model Roncalho AL[1], Ribeiro DE[1], Joca SRL[2] [1]FMRP-USP – Farmacologia, [2]FCFRP-USP – Física e Química

Introduction: According Blier's Theory, the acute administration of SSRI's leads to an increase in serotonin levels and to the activation of the 5-HT1A receptors located in the raphe nuclei, causing an inhibition of the neuronal firing and decreased release of serotonin in postsynaptic areas. With the chronic treatment these receptors are desensitized and the neuronal firing are normalized, inducing the antidepressant effect [1]. Studies have shown an increase of nitric oxide (NO) in patients diagnosed with depression [2] while the decreasing of NO in brain induce antidepressant-like effect [3,4]. Stress is an important componet involved in etiology of depression [5]. Previous studies from our group showed that animals submitted to learned helplessness (LH) model present an increase in nitrate levels in the hippocampus[6]. So, it can be suggested that stressful events are able to induce NOS expression in certain brain regions and the inhibition of this enzyme can leads to antidepressant-like effect. Then the aims of present study are to investigate the behavioral changes and 5-HT1A receptor expression induced by the acute or repeat administration of 7-nitroinidazole (7-NI), an NOS inhibitor in stressed and non-stressed animals. **Methods**: For the behavioral data the animals were exposed to the LH model. In these model, rats were exposed to the pretest session (40 inescapable foot shocks,0.4 mA,10s, 60s ± 30s interval) and acutely or repeatedly treated with imipramine (15 mg/Kg/day,ip) or 7-NI (45 mg/Kg/day,ip).In the 7^{th} day, the animals were exposed to the testing session (30 escapable foot shocks,0.4 mA,10s,60s ± 30s of intervals) and the number of escape failures were recorded.For molecular analysis stressed group were exposed to pretest session of LH as described before, while non-stressed group were just exposed to the LH shuttle box, without the aversive conditions. The hippocampal 5-HT1A receptor expression was analyzed by western blott.**Results** were normalized by GAPDH and apresented as percentage of naïve group. **Results**: The animals pre-exposed to inescapable foot shocks present increased number of escape failures than non-stressed animals. Repeated (but not acute) treatment with imipramine ($H=13,72;p<0.05$) or 7-NI ($H=17,58;p<0.05$) prevented this effect. There were no statistically significant differences between 7-NI and Imipramine groups, reinforcing the 7-NI antidepressant-like effect.Besides, stress protocol increases the the 5-HT1A receptor expressions in ventral hippocampus ($F_{1,39}=4,726;p<0.05$). Treatment or interaction between factors was not different. There were no statistic difference between 5-HT1A recpt expressions in dorsal hippocampus of animals treated with acute or chronic 7-NI.
Conclusion: Corroborating previous data, 7-NI and Imipramine induce antidepressant-like behavior in LH model. Otherside, our work showed for the first time that stress increases the 5-HT1A receptor expression in ventral hippocampus while the treatment during 7 days with 7-NI prevent this effect. References: 1. BLIER,P. The Journ of pharmac and experim therap,v.265 p7,1993 2.LEE,H. Neuropsychob,v.53,p.127,2006 3.JOCA,S.R.L. Psychopharmacology, v.185, n.3,p298,2006 4.WEGENER, G.Brits jour pharm, v.130, n.3,p575,2000 5.HAMMEN, C.Annu. Rev. Clin. Psychol., v. 1, p. 293,2005 6. BIOJONE, C. unpublished data **Financial support**: Capes,CNPq e FAPESP CEUA number :08.1.233.53.5

03.026 Involvement of β-arrestin 2 and G-protein in the effects of nociceptin/orphanin FQ receptor ligands on emotional states in mice. Asth L[1], Ruzza C[2], Malfacini D[2], Medeiros IU[1], Guerrini R[3], Zaveri NT[4], Gavioli EC[1], Calo' G[2] [1]UFRN – Biofísica e Farmacologia, [2]University of Ferrara – Medical Science, Section of Pharmacology and National Institute of Neuroscience, [3]University of Ferrara – Chemical and Pharmaceutical Sciences and LTTA, [4]Astraea Therapeutics, LLC.

Introduction: Nociceptin/orphanin FQ (N/OFQ) is a heptadecapeptide acting as endogenous ligand of N/OFQ peptide (NOP) receptor. Preclinical findings support the involvement of the system in regulating emotional states. This study aimed to investigate the effects of peptide (UFP-113 and [F/G]N/OFQ(1-13)NH_2) and non-peptide (AT-090) NOP partial agonists in mouse anxiety- and depressive-like behaviors as well as in receptor transduction pathways. **Methods:** Male Swiss or CD-1 mice were used together with NOP(+/+) and NOP(-/-) mice. Elevated plus maze (EPM) and forced swim test (FST) were used to evaluate the effects of compounds on anxiety- and depressive-like behaviors, respectively. The ability of NOP ligands to promote NOP interaction with G protein and β-arrestin 2 was evaluated in bioluminescence resonance energy transfer experiments using cell lines permanently co-expressing NOP receptor/luciferase fusoprotein and green fluorescent protein linked to either G protein or β-arrestin 2. NOP partial agonists effects were systematically compared to those of full agonists (N/OFQ and Ro 65-6570) and antagonists (UFP-101 and SB-612111). Non-peptide compounds were injected intraperitoneally (ip) while peptides were injected intracerebroventricularly (icv). **Results:** In EPM, diazepam (1 mg/kg, ip), N/OFQ (1 nmol, icv), Ro 65-6570 (0.1 mg/kg, ip), and AT-090 (0.01 mg/kg, ip) induced anxiolytic-like effects, while UFP-113 (0.01-1 nmol, icv), [F/G]N/OFQ(1-13)NH_2 (0.1-3 nmol, icv), and NOP antagonists were inactive in this assay. In FST, nortriptyline (30 mg/kg, ip), UFP-101 (10 nmol, icv), SB-612111 (10 mg/kg, ip), UFP-113 (0.01 and 0.1 nmol, icv), and [F/G]N/OFQ(1-13)NH_2 (0.3 and 1 nmol, icv) induced antidepressant-like effects, while AT-090 (0.001 - 0.1 mg/kg, ip) and NOP agonists were inactive in this assay. *In vitro*, N/OFQ and Ro 65-6570 behaved as NOP full agonists for G-protein and β-arrestin 2 pathways. AT-090 behaved as NOP receptor partial agonist for both transduction pathways, while UFP-113 and [F/G]N/OFQ(1-13)NH_2 behaved as partial agonists at NOP/G protein and as antagonists at NOP/β-arrestin 2. UFP-101 behaved as NOP receptor antagonist for both transduction pathways. **Conclusion:** NOP ligands producing similar effects (partial agonism) at NOP/G protein interaction, but different effects (partial agonism vs antagonism) at NOP/β-arrestin 2, promote different effects *in vivo* on anxiety and mood. Collectively these results suggest that the action of a NOP ligand on emotional states is better predicted based on its β-arrestin 2 rather than G-protein efficacy. **Support:** CNPq and CAPES Foundation, Brazil (PhD fellowship-Process no 4785-14-2 to LA); University of Ferrara, Italy (FAR grant to GC); NIH grant R43NS070664 (to NTZ); fellowship from the Italian Society for Pharmacology (to CR). **Approval:** Protocols were approved by Ethic Committees for Animal Use of Federal University of Rio Grande do Norte (Protocol No. 21/2013) and of the University of Ferrara and the Italian Ministry of Health (Protocol No. 316/2013-B).

03.027 Activation of CB2 receptors mediates inhibitory effect of rimonabant in the cocaine responses: role of 2-arachinonoylglycerol. Gobira PH, Oliveira A, Gomes JA, Batista EM, Silva FR, Okine BN, Ribeiro FM, Finn DP, Aguiar DC, Moreira FA UFMG

Endocannabinoids anandamide and 2-arachidonoylglycerol (2-AG) act on cannabinoid receptors type one (CB1-R) and type two (CB2-R), through which they modulate the mesolimbic dopaminergic pathway. Most addictive drugs, including cocaine, modulates this neurocircuitry. Accordingly, blockade of CB1-R as well as CB2-R activation inhibit several effects of this psychostimulant. However, a possible interaction between these receptors, have not been investigated. Here we tested the hypothesis that CB1-R blockade shifts endocannabinoid actions to CB2-R and inhibits cocaine effects. Swiss mice (n=7-10/group) received systemic injections of compounds acting on CB1-R and CB2-R followed by cocaine (20mg/Kg). In a first moment, we evaluate total distance travelled and observed that CB1-R blockade, promoted by rimonabant (1, 3 and 10 mg/Kg), prevents cocaine-induced hyperlocomotion. Then, we investigated if this compound would act by shifting endocannabinoid actions to CB2-R. In line with our hypothesis, the CB2-R antagonist, AM-630 (10 and 20mg/Kg), reversed rimonabant-effect. Then we tested if our hypothesis could be extended to effects of increase of c-Fos expression and increase of ERK phosphorylation induced by cocaine. We found that rimonabant inhibited both molecular responses. In line with behavioral results, pretreatment with CB2-R antagonist reverses these effects of rimonabant. To further explore the role of CB2-R, we tested if its activation would mimic the effect of CB1-R blockade. Indeed, the higher dose of the selective agonist, JWH-133 (5, 10 and 20mg/Kg), prevented cocaine-induced hyperlocomotion. We also demonstrated that rimonabant and JWH-133 were effective when combined at sub-threshold doses. To investigate which endocannabinoid would be displaced to CB2-R, we tested the effect of inhibition of endocannabinoids hydrolysis in cocaine-induced hyperlocomotion. Hydrolysis inhibitors of anandamide (URB-597) and 2-AG (JZL184) did not alter this effect. However, when combined with a sub-effective dose of rimonabant, JZL184 (but not URB597) prevented hyperlocomotion. This result suggests the involvement of 2-AG in modulation of cocaine-response, although we did not observe change in endocannabinoid levels of limbic regions after an injection of this psychostimulant. Finally, we test interaction between cannabinoid receptors in conditioned place preference (CPP) protocol. As expected rimonabanto (10mg/Kg) inhibited the acquisition of cocaine-induced CPP. Consistent with our hypothesis, CB2 blockade reversed this inhibitory effect of rimonabant. Conclusion: This study is the first to show that blockade of CB1-R and activation of CB2-R interact to prevent behavioural and neurochemical responses induced by cocaine. We also demonstrated role of 2-AG in this process. Our data suggest a possible mechanism through which modulation in the endocannabinoid system regulates cocaine-responses. Committee for Ethics in Animal Research (Protrocol 242/2013). **Financial support**: CAPES/FAPEMIG

03.028 Effect of Diabetes and Taurine Administration on GABA and glutamate *in vivo* **Efflux in the Hippocampus of rats exposed to the Forced Swimming Test.** Caletti G[1], Henn JG[2], Quinteros D[3], Bandiera S[3], Péres V[2], Barros HMT[1,2], Gomez R[1,3,4] [1]UFCSPA – Ciências da Saúde, [2]UFCSPA – Farmacociências, [3]UFRGS – Farmacologia e Terapêutica, [4]UFRGS – Farmacologia

Introduction: High glucose levels in diabetic individuals promote cellular damage, affecting also the central nervous systems (CNS), increasing the risk of psychiatric disorders, such as depression. Taurine, a semi-essential amino acid, with $GABA_A$ agonist properties, reverses depressive-like behaviors in diabetic rats exposed to the forced swimming test (FST). **Objective**: Because unbalance on GABA and glutamate neurotransmitter systems have been related to major depressive disorders in humans, our objective here was to explore the effect of diabetes condition and chronic taurine treatment on the extracellular concentration of GABA and glutamate, by *in vivo* microdialysis, in the hippocampus of diabetic rats exposed to the FST. **Methods**: Control (CTR) and streptozotocin-induced diabetic (STZ) rats received saline (CTR0, STZ0) or 100 mg/kg taurine (CTR100, STZ100) (n = 4-6/group), intraperitoneally, for 28 days. Microdialysis was performed in the last day of treatment and the extracellular GABA and glutamate were determined by high performance liquid chromatography (HPLC) in the perfusate, collected from the hippocampal area every 30 min for 5.5 h. **Results**: Diabetes condition *per se* did not change baseline GABA and glutamate levels in the hippocampus of rats and taurine treatment did not affect them. However, taurine increased baseline GABA and glutamate levels in control rats. After the FST, the STZ0 rats showed a peak of glutamate and GABA after 30 and 60 min respectively, and the GABA peak was prevented by taurine administration in STZ100, with no changes on glutamate efflux. **Conclusion**: Our results suggest that taurine presents an antidepressant-like effect related to GABA efflux modulation, restoring partially the unbalance in the neurotransmission. Additional studies need to be conducted to explore the taurine efficacy as an adjuvant in the treatment of depression in humans. **Financial support:** CAPES, CNPq, PROPES-UFRGS, UFCSPA - (CEUA-UFCSPA #134/12)