03. Psychopharmacology

03.001

N-acetylcysteine prevents alcohol withdrawal-induced increases in corticosterone and leptin in rats. Schneider RJ[1], Santos CF[2], Clarimundo V[2], Dalmaz C[3,1], Elisabetsky E[2,1], Gomez R[2,1] [1]UFRGS – Neurociências, [2]UFRGS – Farmacologia, [3]UFRGS – Bioquímica

Introduction: N-acetylcysteine (NAC), a glutamate-modulating agent, has been tested in rodents and humans as an anti-addictive substance. However, the effect of NAC in alcohol users or animal models of alcohol withdrawal remains untested. Craving for alcohol has been related to increased levels of serum biomarkers such as corticosterone and leptin. Thus, the aim of this study was to evaluate the effects of NAC on serum corticosterone and leptin levels in rats during alcohol withdrawal. **Methods:** Male Wistar rats were treated with 2 g/kg alcohol (ETOH group: 20% w/v, n = 30) or glucose solution 8% (CTR group, n = 30) by gavage, twice daily, for 30 days. After alcohol cessation, rats were treated for 4 days with NAC or saline (NAC 0, 60, and 90 mg/kg, i.p., n = 10). Twenty-four hours after the last treatment, the rats were euthanized and their trunk blood was collected. The corticosterone and leptin serum levels were determined by ELISA. A two-way ANOVA was performed followed by Tukey's *post-hoc* test and the significance was set at $p<0.05$. The results are presented as the means ± standard error (S.E.M.). (CEUA-UFRGS: # 23069). **Results:** Alcohol withdrawal significantly increased corticosterone levels ($F_{1,29} = 7.87$; $P = 0.010$); treatment with NAC prevented the withdrawal-induced corticosterone increase ($F_{1,29} = 7.14$; $P = 0.004$) in a dose-dependent manner. Alcohol withdrawal significantly increased leptin levels ($P = 0.036$); 4 day treatment with 90 mg/kg NAC prevented ($P = 0.002$) the withdrawal-induced leptin increase. Pearson's test indicates a direct correlation ($r = +0.533$; $P = 0.049$) between the effects of NAC on the corticosterone and on the leptin levels in rats during alcohol withdrawal. **Discussion:** Our results indicate that corticosterone and leptin may be useful as biomarkers to assess relapse risk in alcoholics. In addition, considering that NAC has been shown to possess anti addictive properties in other drugs of abuse and reduced the changes in both biomarkers used in this study, we suggest that NAC may be useful to reduce the risk of drinking relapse in alcoholics. **Financial Support:** CNPq, Capes, Propesq-UFRGS. **Acknowledgements:** Authors are grateful for CNPq (EE, CF, and VC) and Capes (RSJ) fellowships.

03.002

Acute treatment with the cathinone derivative methedrone produces marked behavioral and biochemical changes in mice. Pail PB[1], Costa KM[2], Leite CE[3], Campos MM[4] [1]PUCRS – Cellular and Molecular Biology, [2]PUCRS – Medicine and Health Sciences, [3]INTOX-PUCRS, [4]PUCRS – Dentistry

Introduction: Cathinone derivatives, such as methedrone, are a novel group of recreational psychostimulant substances, commonly denoted as "legal highs" (Gregg & Rawls. Life Sci. 97,27,2013). Herein, we investigated the behavioral and biochemical changes induced by methedrone in mice. **Methods:** The experimental protocols were approved by the local Animal Ethics Committee (Protocol 13/00336). Female C57BL/6 mice (17-22 g) were used. The animals received a single i.p. injection of methedrone (30 mg/kg) and they were initially examined in the open-field test to evaluate general locomotor changes (at 10, 20, 30 and 60 min). On the elevated plus-maze, we recorded the exploration (number of open- and closed-arm entries, and head dipping) and the time spent in open-arms, closed-arms and center platform (at 35 min). Pain threshold was evaluated in the hot-plate test (at 40 min). Depressive effects were assessed in the tail suspension test (TST; at 45 min). To assess the possible mechanisms of action of methedrone, separated groups were pretreated with the non-selective dopamine antagonist haloperidol (0.1 mg/kg, i.p.; 30 min before methedrone), or the 5-HT synthesis inhibitor ρCPA (100 mg/kg, i.p.; one injection a day, four days before methedrone). In additional experiments, the levels of monoamines in *nucleus accumbens*, hippocampus and striatum were determined 20 min after methedrone administration. **Results**: The injection of methedrone resulted in a time-related increase of crossing numbers (125 ± 15%), allied to a marked decrease of grooming (92 ± 1%) and rearing (50 ± 16%), which peaked at 20 min after treatment. Moreover, the treatment with methedrone caused a reduction of time spent in the open-arms (96 ± 2%) and the center platform (62 ± 12%), associated to a significant decrease of exploration index, concerning the head-dipping evaluation (73 ± 21%). The acute administration of methedrone induced an increase of latency in the hot-plate test (74 ± 16%), with a significant reduction of immobility time in the TST (99 ± 1%). Noteworthy, the pretreatment with haloperidol completely reversed the increased number of crossings in the open-field, whereas it prevented methedrone-induced anxiogenic effects in the elevated plus-maze. The depletion of serotonin (5-HT) by ρCPA resulted in a significant reduction in the crossing numbers (35 ± 8%) in the open-field paradigm, and totally inhibited the analgesic-like effects of methedrone in the hot-plate test. Finally, methedrone elicited a 2-fold increase of dopamine levels in the *nucleus accumbens* and striatum, while the elevation of 5-HT levels in the hippocampus and striatum corresponded to 1.5-fold increase. **Discussion:** Acute administration of methedrone induced a series of behavioral changes in mice, as hyperlocomotion, anxiogenic effects, increased latency to thermal stimulation and anti-immobility effects. Methedrone actions appear to rely on dopamine and 5-HT modulation, as demonstrated by pharmacological and biochemical approaches. Other experiments are in progress to further investigate *in vivo* methedrone effects. **Financial Support**: CNPQ, Capes, FINEP, PUCRS.

03.003

Extinction of cocaine-induce conditioned place preference: Temporal characterization

Oliveira-Lima AJ[1], Marinho EAV[1], Malpezzi Marinho EL[2], Jesus PF[3], Hollais AW[3], Aramini TCF[3], Santo R[3], Berro LF[4], Oliveira LC[3], Yokoyama TS[3], Wuo-Silva R[3], Patti CL[3], Frussa-Fillho R[3] [1]UESC – Ciências da Saúde, [2]UESC – Ciências Biológicas, [3]Unifesp – Farmacologia, [4]Unifesp – Psicofarmacologia

The association between drug effects and the environmental context in which these effects are experienced remarkably influences the development and relapse into drug addiction. Therefore, understanding this phenomenon is of major importance regarding clinically relevant strategies. Within this context, we aimed to characterize the extinction and reinstatement of cocaine-environment conditioning on a conditioned place preference (CPP) paradigm. Three-month-old Swiss male-mice were treated during the conditioning phase with daily alternating injections of 20 mg/kg i.p. cocaine (COC) in the paired or saline (SAL) in the unpaired environments for 8 days. Twenty-four hours after the last conditioning session, animals were subjected to a drug-free test with access to both paired and unpaired environments in order to evaluate the development of CPP. Score time (time spent in the unpaired vs paired environments) demonstrated that mice showed preference for the drug-paired environment (208 ± 22 vs 465 ± 41 seconds). After testing (24h), mice were daily freely exposed to the CPP apparatus in drug-free sessions until the complete conditioning extinction. Score time indicated that mice achieved the complete extinction on the fifth re-exposure day. Animals were, then, re-challenged with 20 mg/kg COC, and score time showed a CPP reinstatement (144 ± 37 vs 383 ± 80 seconds). Twenty-four hours later, mice were re-subjected to the extinction procedure. Score time showed that 2 days of drug-free CPP re-exposure were sufficient to re-extinguish the reinstatement-induced conditioning. Taken together, these data provide new understanding of manipulations that can modify the association between COC effects and environmental contexts facilitating the disruption of the addiction phenomenon. **Financial support**: Capes, CNPq, Fapesp, AFIP and FAPESB. CEA-470/09

03.004

Antidepressant-like effect of the extract of *Cecropia obtusa* in mice: Involvement of the monoaminergic system. Schöffer AP[1], Veroneze MH[2], Girardi BA[1], Rubin MA[1] – [1]UFSM – Farmacologia, [2]UFSM –Bioquímica Toxicológica

Several species of *Cecropia* are used in folk medicine for the treatment of various diseases, being widely used by having hypotensive, vasorelaxant, hypoglycemic, analgesic and anti-inflammatory activity. In Brazil the *obtuse* species is used for the treatment of diabetes, anemia, hepatitis and inflammation. In the present study, we investigated the possible antidepressant-like effect of the crude extract of *Cecropia obtusa* and to characterize the participation of the monoaminergic systems in its mechanism of action. Adult male Swiss mice (25-30 g) from the animal house of the UFSM were submitted to two predictive tests of antidepressant property, the tail suspension test (TST) and the forced swimming test (FST). After TST test, locomotor activity was assessed in the open-field test. In the first set of experiments, the effect of the crude extract of *Cecropia obtusa* and the antidepressant fluoxetine (positive control), administered acutely by p.o. route, 60 minutes before TST and FST tests, were investigated. In the second set of experiments, were evaluated the effect of pretreatment of mice with several pharmacological antagonists together with the extract (100 mg/kg, p.o.) to assess the involvement of the monoaminergic systems in the antidepressant-like activity of *Cecropia obtusa*. The effects of the combined administration of sub-effective doses of *Cecropia obtusa* and the antidepressants fluoxetine, imipramine and bupropion were also evaluated. The extract of *Cecropia obtusa* (100 and 300 mg/kg) significantly reduced the immobility time in the TST and in the FST, without changes in locomotor activity in the open-field test, suggesting an antidepressant-like effect. The pretreatment (p.o. 30 minutes before the extract) of mice with ketanserin (5 mg/kg, a preferential 5-$HT_{2A/2C}$ receptor antagonist), prazosin (1 mg/kg, an α_1-adrenoceptor antagonist), yohimbine (1 mg/kg, an α_2-adrenoceptor antagonist), propranolol (2 mg/kg, a β-adrenoceptor antagonist), SCH23390 (0.05 mg/kg, a dopamine D_1 receptor antagonist) or sulpiride (50 mg/kg, a dopamine D_2 receptor antagonist) was able to reverse the anti-immobility effect of the extract (100 mg/kg) in the TST test. The combination of subeffective dose of fluoxetine (5 mg/kg), imipramine (5 mg/kg) or bupropion (5 mg/kg) with a subeffective dose of the extract (30 mg/kg) produced a synergistic antidepressant-like effect in the TST, without locomotor alteration in the open-field test. These data indicates that the extract of the *Cecropia obtusa* has antidepressant-like effect, and that this effect involves the monoaminergic system. The experiments were performed with the approval of the Ethics Committee of the UFSM (process number 116/2013). Financial agencies: CNPq, FAPERGS, Capes, PRPGP-UFSM.

03.005

Arcaine impairs the consolidation and expression of morphine-induced conditioned place preference in mice. Rubin MA, Tomazi L, Schoffer AP, Girardi BA, Mello CF UFSM – Pharmacology

Drug addiction is a chronic relapsing disorder in which compulsive drug-seeking and drug taking behavior persists despite of negative consequences. Several studies have shown that the systemic administration of a variety of N-methyl-D-aspartate (NMDA) receptor antagonists can block the development of conditioned place preference (CPP) induced by rewarding drugs, such as morphine. However, no study has investigated whether polyamines alter abuse-related effects of morphine. In this study we examined the effect of polyamines on CPP and on morphine-induced CPP. Adult male Swiss mice (25-30 g) from the animal house of the UFSM were submitted to the CPP paradigm, an animal model that assess addictive potential of drugs in which environmental cues become associated with the subjective effects of drugs of abuse. On the first and the second days of experiments, each mouse was preconditioned by placing it, once a day, in a CPP apparatus for 15 min, while they could freely access the three compartments of the apparatus. The time spent in each compartment was recorded. Conditioning phase consisted of four consecutive days, with sessions conducted twice each day with 6 h separating each. The duration of each session was 30 min and the mice were confined to the considered compartment, by isolating the compartment using a guillotine door. Animals received morphine, spermidine (a endogenous polyamine that physiologically modulates the NMDA receptor) arcaine (an antagonist of the polyamine-binding site at the NMDA receptor), or saline and immediately were confined to the non-preferred compartment. The post conditioning score was measured in the same way as the preconditioning score. The difference between post and preconditioning scores was considered as change in preference score. Morphine (2.5–10 mg/kg, i.p.) significantly increased the time spent in the drug-paired compartment. Spermidine (3–30 mg/kg, i.p.) and arcaine (0.3 – 3 mg/kg, i.p.) did not induce either CPP or conditioned place aversion. Arcaine (3 mg/kg, i.p.) immediately after conditioning with morphine (5 mg/kg, i.p.), once a day, impaired morphine-induced CPP. Arcaine (3 mg/kg, i.p.) 30 min before testing blocked the expression of morphine-induced CPP. Spermidine (30 mg/kg, i.p.) did not reverse arcaine (3 mg/kg, i.p.)-induced impairment of morphine-induced CPP consolidation and expression. These data indicates that arcaine impairs the rewarding effect of morphine and suggests that the polyamine binding site may be a target to treat morphine abuse. The experiments were performed with the approval of the Ethics Committee of the UFSM (process number 068/2011). **Financial agencies**: CNPq, FAPERGS, Capes, PRPGP-UFSM.

03.006

Anxiolytic effects of cannabidiol administration into the medial infralimbic prefrontal cortex of rats tested in the elevated plus-maze. Marinho ALZ[1], Vila-Verde C[1], Guimarães FS[1] [1]FMRP-USP – Pharmacology

Introduction: The medial prefrontal cortex (mPFC) of rodents consists of several areas, including the prelimbic (PL) and infralimbic (IL) cortex. These adjacent cortical regions have a different cytoarchitecture and partly distinct connections with other brain areas. In a previous study, intra-PL injection of cannabidiol (CBD), a major non-psychotomimetic cannabinoid present in the *Cannabis sativa* plant, induced an anxiogenic-like effect in rats tested in the elevated plus-maze (EPM). This response was prevented by WAY100,635, a $5HT_{1A}$ receptor antagonist. The present study aimed at investigating the effects of intra-IL injection of CBD in rats tested in the EPM. In addition we also verified if intra-IL CBD effects depends on $5HT_{1A}$ receptors. **Methods:** Male Wistar rats had bilateral cannulae implanted into the IL. Five to seven days after surgery the animals were tested in the EPM. Animals received bilateral microinjections of vehicle, WAY100,635 (0.37 nmol) or CBD (15, 30 or 60 nmol) into the IL before being submitted to the behavioral tests. **Results:** Intra-IL injection of CBD (15 and 30nmol) increased the percentage of entries (Vehicle:13.77 ± 3.93, CBD15: 39.76 ± 6.04, CBD30: 41.32 ± 4.30, $F_{(3,26)}$=8,93) and time spent in the open arms (Vehicle:5.70 ± 1.87, CBD15:23.59 ± 4.82, CBD30: 26.51 ± 6.14, $F_{(3,28)}$ =6,90). This anxiolytic response was abolished by previous injection of WAY100,635 (0.37 nmol). No drug changed the number of enclosed arm entries. **Discussion:** Previous studies showed CBD administration into the PL (30nmol) or IL (15 and 30nmol) produced opposite effects on the expression of conditioned fear (Lemos *et al*, 2010). In addition, intra-PL injection of CBD induced anxiogenic effect in rats submitted to the EPM (Fogaça *et al* 2013). On the contrary, the present data indicate that acutely injected cannabidiol into the infralimbic cortex induces anxiolytic responses. These results, therefore, corroborate other findings suggesting that the PL and IL cortices play distinct roles in the modulation of emotional responses. Moreover, as shown on other studies that investigate the acute effects of CBD on emotional responses (Campos *et al*, 2012), they also suggest that these effects depend on facilitation of local $5HT_{1A}$ receptor-mediated neurotransmission. **Financial Support**: CNPq, Fapesp, FAEPA. License Number of the Local Animal Ethical Committee from the School of Medicine of Ribeirão Preto of the University of São Paulo: nº 114/2013. **References:** Campos, A. C. *Philos Trans R Soc Lond B Biol. Sci*, v. 367, p. 3364, 2012. Fogaça, M.V. *Eur Neuropsychopharmacol*, v.10, p.12, 2013. Lemos, J.I. *Behav Brain Res*, v.207, p.105, 2010.

03.007

HU-474, a cannabidiol analogue, attenuates prepulse inhibition impairment induced by MK-801 in mice. Silva NR[1], Gomes FV[1], Pedrazzi JFC[2], Del Bel EA[3], Mechoulam R[4], Zuardi AW[2], Crippa JAS[2], Hallak JEC[2], Guimarães FS[1] [1]USP – Pharmacology, [2]USP – Neurosciences and Behavioral Sciences, [3]USP – Morphology, Physiology and Stomatology, [4]HUJI – Medicinal Chemistry and Natural Products

Introduction: Cannabidiol (CBD) is a non-psychotomimetic compound from *Cannabis sativa* plant that has been reported to produce antipsychotic effects in rodents and humans. However, a limitation to the clinical use of CBD is its low bioavailability, requiring daily doses of up to 1 g to treat schizophrenia patients. In an attempt to overcome this difficulty, chemical modifications in the CBD molecule have been made to increase its potency. Thus, we investigated whether HU-474, a synthetic CBD analogue, would attenuate the impairment in the prepulse inhibition (PPI) test induced by the NMDA receptor antagonist MK-801 in mice. HU-474 effects were compared to those induced by CBD. **Methods:** Male C57BL/6J mice (25-30g) received an intraperitoneal (ip) injection of either vehicle or HU-474 (3, 10, or 30 mg/kg) followed, 30 min later, by a second ip injection of saline (10 mL/kg) or MK-801 (0.5 mg/kg), and were submitted to the PPI test (PPI; pulse: 105dB/20ms; prepulse: 80, 85 and 90dB/10ms, noise: 65 dB) 30 minutes later. The second experiment was similar to previous one except that animals received CBD (15, 30 or 60 mg/kg) followed by MK-801. The Institution's Animal Ethics Committee approved housing conditions and experimental procedures (process number: 058/2013) **Results:** MK-801 impaired PPI in all prepulse intensities (% of prepulse inhibition: VEH + SAL, 80dB: 60.6 ± 3.7, 85dB: 53.4 ± 5.3 %, 90dB: 68.1 ± 2.3 %; VEH + MK-801, 80dB: 6.0 ± 4.8, 85dB: 6.9 ± 5.0 %, 90dB: 13.5 ± 4.7 %). HU-474, at the dose of 30 mg/kg, attenuated the PPI impairment in all prepulse intensities (HU-474 30 mg/kg + MK-801, 80dB: 23.6 ± 4.9 %, 85dB: 28.4 ± 6.8 %, 90dB: 39.0 ± 2.2 %). and was also effective at a dose of 10 mg/kg in the prepulse intensity of 90dB (31.1 ± 4.6 %). CBD, at the doses of 30 and 60 mg/kg, attenuated the disruptive effect of MK-801 only in the prepulse intensity of 90dB (CBD 30 mg/kg + MK-801: 38.5 ± 3.3; CBD 60 mg/kg + MK-801: 36.0 ± 7.3%). CBD and HU-474 by themself did not change PPI (CBD 60 mg/kg + SAL, 80dB: 59.5 ± 4.6 %, 85dB: 67.6 ± 2.6 %, 90dB: 75.1 ± 2.8 %; HU-474 30 mg/kg + SAL, 80dB: 53.9 ± 5.4 %, 85dB: 54.0 ± 3.5 %, 90dB: 62.2 ± 5.6 %). **Conclusion:** These results indicate that, similar to CDB, HU-474 attenuated PPI disruption induced by the administration of an NMDA receptor antagonist. These results suggest that HU-474 could be useful in the treatment of psychotic disorders. **Financial support:** Capes, CNPq, Fapesp, and FAEPA.

03.008

Role of neuronal nitric oxide synthase neurons located in the medial prefrontal cortex on restraint-induced long lasting anxiety in rats. Vila-Verde C, Marinho ALZ, Sonego AB, Guimarães FS FMRP-USP – Pharmacology

Introduction: Neurons expressing the neuronal isoform of the nitric oxide synthase (nNOS) enzyme are located in brain areas related to defensive responses such as the dorsolateral periaqueductal grey, dorsal premammilary nucleus, medial amygdala and medial prefrontal cortex (mPFC). Rats exposed to a live predator (a cat) show increased anxiety and expression of nNOS neurons in the mPFC one-week later. The present study aimed at investigating if restraint stress, another procedure known to induce long-lasting anxiogenic effects, would also be associated with increased nNOS expression in the mPFC. In addition, we also verified if inhibition of this enzyme in the mPFC would be anxiolytic in restrained animals. **Methods:** Male Wistar rats were forced restraint for 3-h. Twenty-four hours or one week later they were tested in the elevated plus maze. Immediately after their brains were removed and nNOS expression in the mPFC was evaluated by immunohistochemistry. Independent groups of animals had bilateral cannulae implanted into the prelimbic (PL) mPFC. Five to seven days after surgery the animals were forced restraint (3-h) and tested in the EPM twenty-four hours later. Ten min before the test they received bilateral microinjections of the selective nNOS inhibitor n-propyl-l-arginine (NPL, 0.04 nmol) or vehicle (saline, 0.2 µL). **Results:** Restraint stress increased (approximately 28% to 49%) the number of neurons expressing nNOS in the prelimbic, but not in the infralimbic, mPFC both 24-h and 7 days after restraint. The number of nNOS neurons was negatively associated with the percentage of open arm entries in the EPM (r=-0.702 and -0.539). Restraint stress decreased open arm exploration 24-h later (percentage of open arm entries, control: 36.2 ± 4.6, restraint:19.8 ± 7.6, $p<0.05$). This effect was prevented by intra-PL microinjection of NPL (drug versus stress interaction, $p<0.05$). **Discussion**: Consistent with our hypothesis, results demonstrate that immobilization stress produces long-lasting (24h and 7 days) anxiogenic effects and this could be related to nNOS expression changes in the prelimbic mPFC. **Financial support:** Fapesp, CNPq, NAPNA-USP, FAEPA. License Number of the Local Animal Ethical Committee from the School of Medicine of Ribeirão Preto of the University of São Paulo: nº006/2013. **References:** De Oliveira, R. W., et. al. *Neurosci Lett*, v. 289, p. 123-126, 2000. Resstel, L. B. M., *et al. Cereb Cortex*,v.18, p. 2027 – 2035, 2007. Campos AC, *et al. Behav Brain Res*, v.256, p. 391– 397, 2013.

03.009

Effects of Euterpe oleracea Mart. (acai frozen pulp) subchronic administration on elevated plus maze behavior testing in Wistar male rats. Kuo J[1], Machado FS[1], Wohlenberg MF[1], Frusciante M[1], Oliveira AS[1], Kneib L[1], Hilger D[1], Medeiros N[1], Dani C[1], Salvador M[2], Funchal CS[1] [1]IPA, [2]UCS – Biotechnology

Introduction: Acai is composed of around seven different species of endemic palms from the *Euterpe* genus, family *Arecaceae*. Among those, *Euterpe oleracea* is the best known species, as it is the main palm for acai harvesting. The leading producer state is Pará, with a production that was of 24 thousand tons at the year of 2010. The aim of this study was to evaluate the effect of subchronic administration of acai frozen pulp in the behavior of male Wistar rats in the elevated plus maze test. **Methods:** Thirty male Wistar rats of 90 days of age (~ 300g) were housed on a standard 12h light:dark cycle with temperature 22 ± 1°C and with free access to water and food. Rats were divided into two experimental groups: Control (water) and treated (Acai pulp). Acai or water were given daily by gavage at a dose of 7 µL/g for 14 days. On the 15th day of the experiment the animals were submitted to the elevated plus maze test. Time and number of entrances in the open and closed arms, as well as number of fecal boli were measured and registered over a period of 5 minutes. Data were analyzed using an unpaired Student's *t*-test by SPSS software, version 17.0. **Results:** It was measured the number of entries in the open and closed arms and fecal boli as well as the time spent in the open and closed arms and the latency to locomotion. No significant results were observed in any of the parameters analyzed ($p>0.05$) between the control group (water) and the Treated group (acai). **Discussion:** The elevated plus maze is a widely used behavioral assay for rodents and it has been validated to assess the anxiogenic or anxiolytic effects of pharmacological agents. An increase in open arm activity (duration and/or number of entries entries) reflects an anxiolytic behavior. Therefore, acai frozen pulp subchronic treatment does not have any anxiogenic or anxiolytic effects observable on Wistar rats, since it was not able to alter the behavior of rats in the elevated plus maze test. All procedures were approved by the Ethics Commission from Centro Universitario Metodista-IPA, protocol number 006/2014. **Financial Support:** Capes, FAPERGS, CNPq.

03.010

Evaluation of the effects of intra-dorsal periaqueductal gray administration of dolasetron in the elevated plus-maze and forced swimming test in rats. Garcia JB, Guimarães RAM, Gavioli EC, Soares-Rachetti VP UFRN – Biophysics and Pharmacology

Introduction: Anxiety and mood disorders are reported as the mental illnesses of most incidences in the world (Beesdo, K. *Arch Gen Psychiatry*, 64, 903, 2007; Kessler, R. C. *Curr Top Behav Neurosci*, 2, 21, 2010). Previous studies have been shown that peripheral administration of 5-HT_3 antagonists generates anxiolytic- and antidepressant-like effects in rodents (Martin, P. *Eur J Pharmacol*, 25, 212, 1992; Kurhe, Y. R. Indian J Farmacol, 46, 100, 2014) and the brain sites for these effects are still unknown. Dorsal periaqueductal gray (DPAG) is a midbrain area extensively associated with the modulation of anxiety and, to a lesser extent, depression responses (Lino-de-Oliveira, C. *Neurosci Lett*, 335, 87, 2002; Zanoveli, J. M. *Eur J Pharmacol*, 473, 153, 2003). This study aimed to investigate the effects of intra-DPAG injection of dolasetron, a 5-HT_3 receptors antagonist, on anxiety and mood-related behaviors in rats. **Methods:** In the experiment 1, male *Wistar* rats (90 days old) received intra-DPAG administration of saline or dolasetron (100ng, 500ng, 1000ng/0.2µl/2min) and, 10 minutes later, rats were submitted to the elevated plus maze (EPM) for 5 minutes. The exploration to open arms in the EPM was employed as an index of anxiety experienced by animals. In the experiment 2, the same doses of dolasetron were injected intra-DPAG (10 min before test) and rat spontaneous locomotion was assessed in the open field test (OFT) for 15 minutes. Twenty four hours later, the same rats were submitted to a cylinder with water during 15 min (pretest) and, 24 hours following the pretest, animals were intra-DPAG injected with dolasetron or saline 10 minutes before being tested in the forced swimming test (FST) for 5 minutes. The time that animals spent immobile in the water or trying to climb the cylinder was assessed in the FST. The experiments were approved by the Ethics Committee on Animal Use – CEUA/UFRN (Protocol N. 049/2013). **Results:** Intra-DPAG administration of dolasetron in rats did not alter the exploration of the open arms in the EPM, when compared to saline group [% of open arms entries (mean ± SEM): saline: 14.47 ± 4.99; 100ng: 12.66 ± 3.92; 500ng: 16.63 ± 2.47; 1000ng: 12.71 ± 4.89, NS]. In the experiment 2, there were no differences between groups on the locomotion parameters in the OFT [Distance travelled (m): saline: 17.81 ± 3.02; 100ng: 13.76 ± 2.3; 500ng: 24.73 ± 7.54; 1000ng: 13.95 ± 4.54]. Also, in the FST, there were no differences between saline group and dolasetron groups on the immobility and climbing parameters [immobility (sec): saline: 136.78 ± 21.22; 100ng: 120.87 ± 16.72; 500ng: 162 ± 28.73; 1000ng: 106.33 ± 43.21, NS]. **Discussion**: The administration of dolasetron, a 5-HT3 receptors antagonist, intra-DPAG in the doses of 100, 500 and 1000ng did not alter behaviors generated by the exposure to the elevated plus-maze, open field and forced swimming tests in rats. The lack of effect of this antagonist could suggest that, under physiological conditions, activation of 5-HT3 receptors in the DPAG is not required for the expression of the behaviors related to anxiety, locomotion and depression. **Financial support**: Capes

03.011

Antinociceptive activity of two analogues structural eugenol. Fonseca DV[1], Salgado PRR[1], Muniz VM, Santos AKFS, La Rocca V, Carvalho FL, Salvadori MGSS, Barbosa Filho JM, Almeida RN CCS-UFPB

Introduction: The eugenol is a phenylpropanoid present in many herbs. This compound exhibits wide variety of biological properties such as anticonvulsant, antioxidant, anti-inflammatory activity and has been widely used as an anesthetic in dentistry. In this study, we investigated the possible antinociceptive effect of the two structural analogues, 2-Allyl-6-methoxyphenol (AE-1) and 4-Allyl-1,2-methylenedioxybenzene (AE-2), the acetic acid induced writhing test. **Methods**: *Swiss* albino male mice (3 months old, 25-35g) were divided into four groups (n=8) which received following treatments by intraperitoneal (i.p.) route: vehicle (control group), AE-1 (50 mg/kg), AE-2 (50 mg/kg) or morphine (6 mg/kg). Thirty min after the administration, the animals received acetic acid (1%) 1% in distilled water (0.1 mL/10 g) and placed in individual polyethylene boxes. After 5 minutes, was then recorded the number of contortions displayed by each animal during a period of 10 minutes of observation. All experiments were approved by the Ethics Committee for Animal Research of the Laboratory of Pharmaceutical Technology of UFPB (protocol number 0201/13). Values are expressed as mean ± S.E.M. ($p<0.05$). **Results and discussion:** In the writhing test, the result indicated that treatment with AE-1 at dose of 50 mg/kg (552.1 ± 98.1**s) and morphine (6 mg/kg) (749.8 ± 87.2***s) significantly increased the latency of writhing, when compared to the control group (215.8 ± 18.4), while AE-2 50 mg/kg (420.9 ± 72.0s) did not have this effect. When evaluating the number of writhings, AE-1 50 mg/kg (5 ± 2) and AE-2 50 mg/kg (10 ± 2) were able to inhibit this parameter evaluated and morphine (1 ± 1) when compared to the control group (24 ± 3). In summary, the results demonstrate that AE-1 and AE-2 have the antinociceptive effects in mice. These results justify the continuation of research in search of possible mechanisms of action. **Financial Support:** CNPq.

03.012

Activation of CB1 receptor in dorsomedial hypothalamus (DMH) induces antiaversive effect in rats. Bastos JR[1], Viana TG[2], Aguiar DC[2], Moreira FA[2] [1]UFMG – Neurociências, [2]UFMG – Farmacologia

Introduction: Glutamate plays a role in defensive responses, facilitating aversive reactions in several brain regions, including the DMH. On the other hand, the endocannabinoid system can reduce glutamatergic activity and inhibit the panicogenic-like effect caused by this excitatory amino acid. The aim of this work is to evaluate if the facilitation of the endocannabinoid system could modulate aversive responses induced by NMDA, a glutamatergic agonist. **Methods:** Male Wistar rats (280-320g; n=6-7/group) were submitted to stereotaxic surgery for cannula implantation targeting the DMH. After recovery, they received local injections of vehicle or 3 different doses of NMDA (1.0; 3.0; 10.0 nmol/0.2µL) and were immediately placed in an acrylic box, where the behavior was recorded during 5 minutes. In independent experiments, they received drug injections 10 minutes before NMDA 10 nmol: ACEA, CB1 agonist (0.005; 0.05; 0.5 pmol); URB597, anandamide-hydrolysis inhibitor (0.3; 1; 3 nmol) or URB602, 2AG-hydrolysis inhibitor (0.3; 1; 3 nmol). The data were analyzed by Kruskall-Wallis followed by Mann-Whitney test. **Results:** NMDA 10 nmol induced aversive responses, characterized by an increase in the number of crossings and jumps (p=0.0025; Mann-Whitney for variables). ACEA reduced the number of crossings and jumps induced by NMDA (p=0.0122, Kruskall-Wallis). URB597 and URB602 were not efficacious in reducing crossings (p=0.0654 and p=0.0592, Kruskall-Wallis, respectively) or jumps (p= 0.0691 and p= 0.0683, Kruskall-Wallis, respectively) **Discussion:** These results show that only the direct activation of CB1 receptor in the DMH prevents NMDA-induced aversive behaviors. Local inhibition of endocannabinoid-hydrolysis is not able to mimic this effect. This is in contrast with results obtained after injections into the dorsal periaqueductal gray, in which URB597 and URB602 preventes the aversive effects of NMDA. Our hypothesis is that the escape response in the DMH is not enough aversive to recruit endocannabinoids. Further experiments are under way to evaluate if activation of CB1-positive neurons occurs during these responses. We thank CNPq for the Financial support. CETEA 059/11

03.013

Effects of ayahuasca on the development of ethanol-induced behavioral sensitization and on a counter-conditioning strategy in mice. Marinho EAV[1], Oliveira-Lima AJ[1], Santos R[2], Hollais AW[2], Wuo-Silva R[2], Yokoyama TS[3], Malpezzi-Marinho ELA[4], Ribeiro-Barbosa PC[5], Berro LF[6], Frussa-Filho R[2] [1]UESC – Ciências da Saúde, [2]Unifesp – Farmacologia, [3]Unifesp – Fisiologia, [4]UESC – Ciências Biológicas, [5]UESC – Filosofia e Ciências Humanas, [6]Unifesp – Psicobiologia

Introduction: hallucinogenic drugs were used to treat alcoholic patients in the past, and recent evidence suggests that ayahuasca (Aya) may have therapeutic effects on addiction. **Aims:** we investigated the effects of Aya on spontaneous locomotion and Eth-induced hyperlocomotion and locomotor sensitization by a 2-injection protocol in mice. We also tested the effects of Aya on a counter-conditioning protocol after a repeated Eth treatment. **Methods:** Braz Cubas University Ethical Committee (#176/2008) approved all procedures. Aya solution was obtained from Santo Daime, and liquid was lyophilized. Eth and Aya were diluted in saline (Sal) and solutions were given intraperitoneally at a volume of 10 ml/kg of body weight. *Exp. 1*: 80 3-month-old Swiss male mice were habituated to the open-field (OF) for 2 days. On Day 3, mice were treated with Sal (n=30) or Aya (30, 100, 200, 300 or 500 mg/kg, n=10 per group) followed by exposure to OF 30 min later to locomotor activity (LA) quantification (LAQ, 10 min). Once removed from the OF, 20 animals from the Sal group received Sal injection and the other 10 mice and all those treated with Aya received 1.8 g/kg Eth, being 5 min later re-exposed to OF for LAQ. The following groups were formed: Sal-Sal, Sal-Eth, Aya30-Eth, Aya100-Eth, Aya200-Eth, Aya300-Eth and Aya500-Eth. On Day 10, 10 out of 20 animals from the Sal-Sal group received a new Sal injection (Sal-Sal-Sal group) and the remaining 10 mice received 1.8 g/kg Eth (Sal-Sal-Eth group). Eth was also administered to all other animals for the 2nd time. Five minutes later, mice were placed in OF for LAQ. *Exp. 2*: 66 mice were habituated to OF for 2 days. From Day 3, animals received Sal or 1.8 g/kg Eth (n=33 per group) 5 min prior to being placed in OF every other day for 15 days (Days 3 to 17, Eth-induced behavioral sensitization/conditioning phase). From Day 19, for 8 consecutive days (Days 19 to 26), 11 animals from Sal group received daily Sal injections and the other 22 received daily Aya injections at the doses of 100 or 300 mg/kg (n=11 per group). Eth-conditioned groups underwent the same procedure. Thirty minutes later, mice were exposed to OF (10 min, counter-conditioning phase). The following groups were formed: Sal-Sal, Sal-Aya100, Sal-Aya300, Eth-Sal, Eth-Aya100 and Eth-Aya300. On Day 30, all animals received a Sal injection, being 5 min later placed in the OF for LAQ. On Day 32, animals were tested for reinstatement of Eth-induced behavioral sensitization, receiving an injection of 1.8 g/kg Eth and being 5 min later placed in the OF for LAQ. **Results:** *Exp. 1*: 1-way ANOVA revealed that previous treatment with Aya at all doses prevented the development of Eth-induced locomotor sensitization (Day 10: Aya-Eth-Eth groups LA <Sal-Eth-Eth LA) without modifying spontaneous locomotor activity. The highest doses of Aya also showed selectivity to both Eth-induced hyperlocomotion and locomotor sensitization, inhibiting the acute Eth effect (Day 3: Aya300-Eth and Aya500-Eth LA <Sal-Eth LA) and its subsequent locomotor sensitization to a second Eth injection. *Exp. 2*: 2-way ANOVA revealed that an 8-day counter-conditioning with 100 or 300 mg/kg Aya was effective in blocking the subsequent drug-induced reinstatement of locomotor sensitization to Eth (Day 32: Eth-Aya100 and Eth-Aya300 LA <Eth-Sal LA). **Conclusions:** Aya inhibited the initiation and development of Eth-induced behavioral sensitization, also showing effectiveness in preventing its reinstatement when

administered in the Eth-associated environment. **Funding:** Fapesp, CNPq, Capes and AFIP.

03.014

Evaluation of the effect of pregabalin on anxiety-like behaviors in female rats. Souza AF, Mendes CRM, Soares-Rachetti VP, Gavioli EC UFRN – Biofísica e Farmacologia

Introduction: Considering disadvantages presented by anxiolytic drugs clinically used, such as benzodiazepines, which promote dependence (Kavoussi, R., *Eur Neuropsychopharmacol*, vol.16, p.128, 2006) and antidepressants, whose latency for therapeutic effect is approximately three weeks (Moreno, R.A., *Rev Bras Psiquiatr*, vol 21, p.24, 1999), the evaluation of the effects of new drugs in experimental animal models becomes a useful tool to identify new potentially anxiolytic substances. The aim of present study was to investigate the effects of pregabalin, an analog of the neurotransmitter GABA and a highly selective, high-affinity ligand of the α2-δ subunit of the P/Q type of voltage-dependent calcium channels (Micó, J.A., *CNS Drugs*, vol.26, p.637, 2012; Taylor, C. P. Epilepsy. Res., vol.73, p.137, 2007) in anxiety-related behaviors in the rats elevated plus-maze test (EPM, Pellow, S., J *Neurosci* Methods, vol.14, p.149, 1985). **Methods:** Female *Wistar* rats (± 90 days old) weighing 220-250g were submitted to the mapping of the estrous cycle ten days preceding the test. In the day of the behavioral test, were administered (p.o.) with vehicle or Pregabalin (PGB, (S)-3-(aminomethyl)-5-methylhexanoic acid, Lyrica®) at doses of 75, 150 or 300 mg/kg/ml sixty minutes prior to the EPM. The number of females at early diestrus, late diestrus, proestrus and estrus was balanced for each treatment group. The exploration of the open and closed arms of the EPM was registered for 5 minutes. This study was conducted after approval of local Ethical Committee (protocol nº 050/2013). **Results:** Results show that pregabalin at the doses of 75, 150 and 300 mg/kg did not alter entries in the enclosed arms of the EPM [(mean ± SEM) control: 7.93 ± 1.03; PGB75: 7.44 ± 0.91; PGB150: 6.90 ± 1.18 and PGB300: 3.71 ± 0.96; $F(3,41)=2.37$; $p=0.08$; ANOVA, n=7-15]. Also, these doses of pregabalin altered neither the time nor the total entries in the open and enclosed arms of the EPM [(mean ± SEM of total entries in the open and enclosed arms of the EPM) control: 13.46 ± 1.41; PGB75: 14.11 ± 1.88; PGB150: 13.63 ± 2.18 and PGB300: 8.85 ± 1.77; $F(3,41)=1.31$; $p=0.28$; ANOVA, n=7-15]. When analyzed the percentage of entries in the open arms, pregabalin did not modify this parameter [(mean ± SEM) control: 20.20 ± 2.38; PGB75: 22.97 ± 1.56; PGB150: 24.47 ± 2.46 and PGB300: 29.44 ± 2.51; $F(3,41)=2.32$; $p=0.09$, ANOVA, n=7-15]. Regarding the percentage of time spent in the open arms of the EPM, ANOVA did not show differences between groups [(mean ± SEM) control: 24.81 ± 4.40; PGB75: 34.14 ± 7.84; PGB150: 29.57 ± 5.05; PGB300: 25.80 ± 4.68; [$F(3,41) = 0,57$; $p = 0,63$; ANOVA]. **Discussion:** The results obtained at our experimental conditions suggest that the administration of pregabalin at doses of 75, 150 and 300 mg/kg in female rats does not alter anxiety-related behaviors or locomotion in the EPM test. **Financial support**: PPG-UFRN and Capes

03.015

Reciprocal roles for CB1 and CB2 cannabinoid receptors in cocaine-induced hyperlocomotion Gobira PH, Moreira FA UFMG – Farmacologia

Introduction: Type-one (CB1-R) and type-two (CB2-R) cannabinoid receptors are responsible for the pharmacological effects of ?-9-tetrahydrocannabinol, the main active compound from *Cannabis sativa*. Their endogenous ligands, termed endocannabinoids, act upon the brain dopaminergic mesocorticolimbic system, which is directly or indirectly targeted by most addictive drugs. The possible interactions between CB1-R and CB2-R, however, have remained to be investigated. Thus, this study was designed to test the hypothesis that CB1 blockade shifts endocannabinoid actions to CB2-R and inhibits cocaine-induced hyperlocomotion. **Methods and Results:** Male Swiss mice (n=7-10/group) received systemic injections of compounds acting on CB1-R and CB2-R followed by cocaine (20 mg/kg). The total distance travelled was automatically recorded in an arena and analyzed by ANOVA followed by Newman-Keuls test. First, we tested whether the CB1-R blockade prevents cocaine-induced hyperlocomotion and found that the antagonist/inverse agonist, rimonabant (1, 3 and 10 mg/kg), was effective at the higher dose. In the second experiment, 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 20 mg/kg), reversed the effects of rimonabant (10 mg/kg). 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 20 mg/kg), prevented cocaine-induced hyperlocomotion. Finally, we demonstrated that rimonabant and JWH-133 were also effective when combined at sub-threshold doses (3 and 10 mg/kg). None of the compounds induced changes in basal locomotion. **Conclusion:** Our results demonstrate that CB1-R blockade and CB2-R activation interact to prevent cocaine-induced hyperlocomotion. This represents a possible mechanism though which the endocannabinoid system modulate the effects of this psychostimulant drug. Approved by the Committee for Ethics in Animal Research (Protrocol 242/2013). **Financial support**: Capes/FAPEMIG

03.016

Involvement of alpha-1B-adrenoceptors in the anti-immobility effects of imipramine in the tail suspension test. Ribeiro ASR, Pupo AS IBB-Unesp-Botucatu – Pharmacology

Introduction: Imipramine is a tricyclic antidepressant non-selective inhibitor of norepinephrine and serotonin neuronal reuptake. The α1-adrenoceptor (α1-AR) subtypes targeted by the increased synaptic levels of norepinephrine induced by imipramine in the central nervous system are unknown. This study investigates the involvement of α1-AR subtypes in the behavioral effects induced by imipramine in the tail suspension test. **Methods:** All procedures were approved by the local Ethics Committee on Animal Use – CEUA (protocol number 418). Male Swiss mice were treated (i.p.) with vehicle, imipramine (IMI – 32 mg/kg), prazosin (non-selective α1-AR antagonist, PRA – 0.25 to 1 mg/kg), BMY-7378 (selective α1D antagonist, BMY – 0.25 to 2 mg/kg), RS-100329 (selective α1A antagonist, RS – 0.1 to 4 mg/kg), L-765314 (selective α1B antagonist, L76 – 0.25 to 2 mg/kg) or the association "antagonist" plus imipramine, 30 minutes before submitted to the tail suspension test. Total immobility time was recorded during an observation window of 6 minutes. Data are presented as mean ± standard error of mean and significant differences ($p \leq 0.05$) between means were tested by ANOVA followed by Dunnett test for multiple comparisons. **Results and Discussion:** As expected, the immobility time found in mice treated with IMI (52 ± 11 s) was much lower than that presented by mice treated with vehicle (133 ± 13 s). However, the immobility time of mice treated with IMI + PRA (170 ± 24 s) was not different from that found in mice treated with vehicle (133 ± 13 s). These results indicate an important contribution of α1-ARs in the effect of IMI in the immobility time. The immobility time of mice treated with IMI + BMY-1 (39 ± 11 s) was not different from that observed in mice treated with IMI alone (34 ± 7 s), indicating that the effect of imipramine does not depend on α1D activation. Similarly, the immobility time found in mice treated with IMI + RS-1 (52 ± 14 s) was not different from that found in mice treated only with IMI (54 ± 10 s). This indicates that the α1A subtype is not the target for the increased synaptic levels of norepinephrine. On the other hand, the immobility time of mice treated with IMI plus the α1B selective antagonist L76-1 was not different from that presented by mice treated with vehicle (79 ± 12 and 114 ± 10 s/, respectively), indicating that the α1B subtype is involved in the effect of imipramine. In addition, both RS and BMY, but not L76, presented antidepressant-like effects when given alone, as mice treated with these drugs showed reduced immobility times in comparison to mice treated with vehicle; these results point that the selective antagonism of α1A and α1D, but not of α1B, results in antidepressant effects. In conclusion, α1-AR subtypes have opposing roles in mice behavior in the tail suspension test; selective activation of the α1B associated with α1A and α1D antagonism might be one of the mechanisms involved in the antidepressant activity of imipramine. **Financial support**: Capes, Fapesp (08/50423-7 to ASP)

03.017

5-HT2C receptors of the dorsal periaqueductal gray and the anxiety-modulating effects of antidepressant drugs. Costa HHV[1], Vicente MA[2], Casarotto PC[1], Zangrossi HJr[1] [1]FMRP-USP, [2]FCFar-Unesp

Introduction: Activation of 5-HT2C receptors in structures such as the basolateral amygdala (BLA) and dorsal periaqueductal gray (dPAG) increases the expression of anxiety-related behaviors. Recently, it has been shown that the blockade of BLA 5-HT2C receptors cancels the anxiogenic effect caused by acute administration of antidepressant drugs (ADs) such as imipramine and fluoxetine [1]. In this study we investigated whether the blockade of 5-HT2C receptors in the dPAG also interferes with the anxiogenic effect caused by acute administration of fluoxetine. We also investigated whether chronic treatment with imipramine and fluoxetine changes the number of 5-HT2C receptors in the dPAG and BLA. **Methods:** A guide cannula was implanted in dPAG of male Wistar rats. Seven days after surgery, the animals were injected intra-dPAG with the 5-HT2C receptor antagonist SB-242084 (10nmol) or saline, ten minutes later fluoxetine (15 mg/kg) or vehicle solution was intraperitoneally injected and thirty minutes after, the rats were submitted to the Vogel conflict test. To analyze possible changes in receptor number, another group of animals were treated with fluoxetine (10 mg/kg) or imipramine (15 mg/kg) for 21 days and then the tissue was collected for 5-HT2C receptor quantification by western blotting. **Results:** Systemic injection of fluoxetine reduced the number of punished licks in Vogel conflict test and this anxiogenic effect was not altered by prior injection of SB-242084 into the dPAG. The western blotting analysis showed that whereas chronic treatment with fluoxetine or imipramine did not change the number of 5-HT2C receptors in the dPAG, in the BLA the number of these ligand sites was significantly reduced. **Discussion:** Our results indicate that 5-HT2C receptors located in the dPAG do not participate in anxiogenic-like effect caused by acute administration of fluoxetine. The decrease in the number of 5-HT2C receptors in the BLA corroborates previous behavioral results obtained by our research group, indicating that these receptors are desensitized after chronic administration of ADs [2]. **Financial support**: Fapesp (Process Number 2013/05903-9). Protocol Number: 34/2013 (Animal Ethics Committee of the University of São Paulo). **References**: [1] Vicente, MA. *Int J Neuropsychopharmacol.*, 15, 389, 2012. [2] Vicente, MA. *Neuropsychopharmacology*, 79, 127, 2014.

03.018

Arachidonoyl serotonin, a dual blocker of fatty acid amide hydrolase and transient receptor potential vanilloid type-1 channels, reduces the expression of contextual fear conditioning via CB1 receptors. Oliveira AC, Gobira PH, Moreira FA UFMG – Pharmacology

Introduction: Anandamide(AEA) is the best characterized endocannabinoid who exerts their actions through interaction with CB1 and CB2 cannabinoids receptors beside the vanilloid receptor, TRPV1. Studies showed that the blockade of enzyme fatty acid amide hydrolase (FAAH), which is responsible by anandamide hydrolysis, reduces anxiety-like behaviors at low doses, and can exacerbates them at high doses, and this latter effect is blocked by a TRPV1 antagonist. Recently a drug (AA-5-HT) that acts as a dual blocker to FAAH and TRPV1 was development and showed anxiolityc-like responses in elevated plus maze test. The aims of this present work were investigate if this drug would show a similar behavior in a contextual fear conditioning, and compare these effect with drugs that block individually FAAH and TRPV1. **Materials and Methods:** On the first day Swiss mice were pre-exposure to conditioning box for three minutes, after this time three electric footshocks of 0.6 mA/2 s were delivered at 20 s to 1 min intervals, after the last shock the animals stay for more one minute in the box and then were put back in their home cage. In the second day they were re-exposures for 5 min to the same conditioning box, but without any shock presentation, and we evaluated the time that these animals exhibit freezing behavior. Thirty minutes before the re-exposures protocol mice received the following treatments; Experiment 1: vehicle (Veh.) or three doses of AA-5-HT (0,1/0,3/1,0 mg/kg), Experiment 2: Veh. and three doses of a FAAH inhibitor, URB 597(0,1/0,3/1,0 mg/kg); Experiment 3: Veh. or three doses of TRPV1 selective blocker, SB366791(0,1/0,3/1,0 mg/kg); Experiment 4: Veh + Veh. or AM 251(a CB1 selective antagonist) + Veh., or AM251 + AA-5-HT or VEh. + AA-5-HT. **Results:** The one way ANOVA showed that three doses of AA-5-HT reduced the freezing behavior, suggesting a anxiolytic-like effect of this drug($F_{(3,32)} = 4.2$, $p = 0.018$; Newman-Keuls, $p<0.05$ compared to vehicle group). A similar effect was observed with higher dose of URB 597 $F_{(3,29)} = 4.1$, $p = 0.15$; Newman-Keuls, $p<0.05$ compared to vehicle group). The treatment with SB366791was not statistically significant ($F_{(3,30)} = 1,9$, $p = 0.014$; Newman-Keuls, $p > 0.05$ compared to vehicle group). And finally the pre-treatment with CB1 antagonist was able to reverse the effect induced by AA- 5-HT($F_{(3,30)} = 3,5$, $p = 0.025$; Newman-Keuls, $p<0.05$ compared to vehicle group). **Conclusion:** Our dates suggest that dual blocker of FAAH and TRPV 1 channels promoted an anxiolytic-like effect, which was reversed by pretreatment with CB1 receptor antagonist. In addition we find that AA-5-HT was more potent than selective blockers of FAAH or TRPV1. **Financial support**: Capes/Fapemig. Experimental Committee for ethics in experimental research: 250/2010

03.019

Effects of resveratrol on fluphenazine-induced vacuous chewing movements in male and female rats. Busanello A[1], Freitas CM[2], Leal CQ[3], Bressan GN[3], Barbosa CP[3], Krum BN[3], Reis EM[1], Barbosa NVB[2], Fachinetto R[1] [1]UFSM – Farmacologia, [2]UFSM – Bioquímica Toxicológica, [3]UFSM – Farmácia

Introduction: Treatment with classical neuroleptics in humans can produce a serious side effect, known as tardive dyskinesia (TD). Resveratrol, a polyphenol compound contained in red grapes and red wine, exhibits a wide range of biological activities including the protection of cultured neurons against oxidative stress (Blanchet *et al.*, 2008). Resveratrol is structurally related to the syntheticestrogen, diethylstilbestrol and, some authors suggest that the effects of resveratrol can be gender-specific (Di Liberto *et al.*, 2012). Here, we examined the possible neuroprotective effects of resveratrol, in an animal model of orofacial dyskinesia (OD) induced by acute treatment with fluphenazine comparing its effects in male and female rats. **Methods:** Adult male and females rats were treated during 3 weeks with control (received vehicle of fluphenazine and vehicle of resveratrol), resveratrol (received vehicle of fluphenazine and resveratrol), fluphenazine (fluphenazine and vehicle of resveratrol) and fluphenazine + resveratrol (received fluphenazine and resveratrol). Fluphenazine enantate was administered at a dose of 25 mg/kg, i.m., in single administration in the first day of the experiment and resveratrol was administered at a dose of 10 mg/kg, i.p., every day. Vacuous chewing movements (VCMs), locomotor and exploratory performance were evaluated on day 21. Data were analyzed by one-way ANOVA followed by Tukey test when appropriated. Results were considered statistically significant when $p<0.05$. The experimental protocol was approved by internal ethical commission of UFSM under the number 091/2013. **Results and discussion:** Statistical analysis revealed that fluphenazine administration caused a marked increase on VCM intensity when compared with its vehicle in male ($F(3,28)=5.36$, $p<0.05$) and female rats ($F(3,27)=19.19$, $p<0.05$). Co-treatment with resveratrol did not modify the VCM intensity. We also analyze the prevalence of OD (represented by number of animals presenting more than 30 VCM). Fluphenazine treatment produced VCM in 50% of male and 90% of female rats and the concomitant treatment with resveratrol decreased the prevalence to 30% in male and to 50% in female rats, but did not modify the intensity of VCMs in those rats that developed VCMs. Furthermore, the fluphenazine administration reduced the locomotor (Male ($F(3,28)=26.7$; $p<0.05$), Female ($F(3,27)=44.85$); $p<0.05$) and exploratory (Male ($F(3,28)=40.40$; $p<0.05$), Female ($F(3,27)=79,34$); $p<0.05$) activity of animals in the open field test. Resveratrol co-treatment was not able to protect the reduction of both parameters. Taken together, our data suggest that resveratrol was more effective in to reducing only the prevalence of VCM in female than in male rats, suggesting an effect dependent on the gender. **Financial support**: CNPq, FAPERGS, Capes and UFSM. **References:** Blanchet, J. *et al.*, *Prog. Neuropsychopharmacol. Biol. Psychiatry*, 32:1243, 2008. Di Liberto, V. *et al*, *Neuropharmacology*, 62:1011, 2012.

03.020

Antidepressant-like effect of *Croton zehntneri* essencial oil (OECz) in mice. Custódio FR, Oliveira PLN, Liberato FR, Melo CTV NUBEM-INTA

Introduction Depression is a serious mood disorder that affects up to 20% of the world population and may result in major social and economic consequences. Although significant progress has been made in research for treating depression, the therapeutic responses are still unsatisfactory. Thus, medicinal plants have been studied in order to investigate their potential as treatment of depression. *Croton zehntneri* is a native plant of Northeast region of Brasil, popularly known as *canelinha*, and it is largely used in folk medicine as an appetite stimulant, analgesic, sedative and anxiolytic. Therefore, the aim of this study is to investigate if OECz presents antidepressant-like effects on animal models of forced swimming, tail suspension and open field tests. **Methods** Female mice (20-25g) were divided into 4 groups of 5-7 animals per group for each test: controls (vehicle – tween 80 1%), OECz-100 (OECz 100 mg/kg), OECz-200 (OECz 200 mg/kg) and FLU-35 (fluoxetine 35 mg/kg) or DZP-2 (diazepam 2 mg/kg). Fluoxetine was used as standard in forced swimming and tail suspension tests and diazepam was used in the open field test. OECz, FLU and vehicle groups were administered by gavage and DZP group received intraperitoneal (i.p.) injection. After 30 minutes of i.p. injection and 60 minutes after gavage administration, mice were submitted to experimental tests. In the forced swimming, animals were placed in a water tank and left there for five minutes to observe the immobility time. In the tail suspension test, mice were suspended by the tail and the immobility time was recorded over a period of 6 min. In the open field test, the number of crossings was accounted for 5 min representing the locomotor activity. Data were analyzed by One way ANOVA followed by Student Newman Keuls as the *post hoc* test. Data are here presented by mean ± S.E.M (number of animals). Ethical approval was obtained from the Ethics Committee on Animal Research (CEUA) of *Instituto Superior de Teologia Aplicada* – INTA with the protocol number 2013.07.002-P. **Results** In the forced swimming test, only OECz-200 decreased immobility time at 33.72% (84.83 ± 10.49(6)) as compared to vehicle (128.0 ± 6.25(5)). OECz did not altered the immobility time in the tail suspension test. Furthermore, OECz was not able to modify the number of crossings in the open field test, thus it did not altered the locomotor activity. FLU-35 and DZP-2, as expected, decreased all parameters analyzed in all tests comparing to respective controls. **Discussion:** The results showed that OECz presented antidepressant-like effect only with the higher dose on the forced swimming test and this effect is specific once the locomotor activity was not modified in the open field test, similarly to antidepressant drugs. On the other hand, the antidepressant-like effect was not corroborated in the tail suspension test, but it can be explained considering that the forced swim test is more sensitive to antidepressant drugs than the tail suspension test. Moreover, the number of animals may have been too small to detect effects with lower dose of OECz due to high variability in the animal behavior. **Acknowledgments:** Grateful to INTA for the Financial support

03.021

Analysis of prescriptions with potential drug interactions in Hospital of Pediatrics Professor Heriberto Ferreira Bezerra (HOSPED), Natal RN. Pinto MNDS[1], Carvalho MDS[1], Cabral CHK[2] [1]DBF-UFRN – Biophysics and Pharmacology, [2]HOSPED-UFRN

Introduction: Drug interactions occur when the actions of a drug are altered by the presence of another drug, such interactions may result in synergistic or antagonistic effects, which can lead to decreased efficacy or even therapeutic failure, or even increased pharmacodynamic effects producing adverse drug events. **Methodology**: This was an observational cross-sectional quantitative study was retrospective, where we analyzed 1,706 prescriptions relating to 229 patients for two months, including April and May 2012, the interactions were classified according to the risk: **C**, **D**, **X**, according to the database Uptodate®. **Results and discussion:** Of the prescriptions analyzed, 559 (32,76%) had at least one clinically significant drug interactions, the majority of this total (255,45.6%) showed only a single interaction of clinical importance, 125 prescriptions (22.4%) presented two interactions, 75 (13.4%) had three interactions and 104 (18.6%) had more than three interactions. Altogether 173 clinically significant drug interactions were detected, this total has been found 144 interaction risk C, 28 risk D and one interaction risk X, these interactions were classified according to UpToDate data base. The interactions the most frequent risk C in Prescriptions were ceftazidime x amikacin; furosemide x captopril, and furosemide x salbutamol with 3.47% each. interactions the of risk D was more frequent with Diazepam x Phenobarbital 2.89%, the only interaction of the risk x was found among Propanolo x Salbutamol. **Conclusion**: the prescriptions containing drug interactions most showed only an interaction among the interactions detected the majority were C where risk management is to monitor the patient. Thus, the multidisciplinary team, especially physicians and pharmacists should be aware of the parameters will monitor the patient. **Acknowledgments**: Hospital of Pediatrics Professor Heriberto Ferreira (HOSPED). **References:** Interactions 2nd Edition, Kenneth A. Bachmann, PhD, *et al.* 2006. Silva, NMO *et al*, Evaluation of potential drug interactions in prescriptions for admitted patients in public hospital specializing in women's health, in Campinas-SP. *Rev Cienc Farm Primary Apl*, 2010.; 31 (2): 171-176. Drug interactions, 2013 Available at: <http://www.uptodate.com/crlsql/interact/frameset.jsp>. Accessed on May 15, 2014.

03.022

Investigation of behavioral changes of pentoxifylline in rats. Garantizado CR[1], Cavalcante ALC[2], Lima FAVL[3], Calou IBF[4], Siqueira RMP[1] [1]FAMETRO – Farmácia, [2]UNIFOR – Medicina, [3]UFC – Farmacologia, [4]UFPI

Introduction: Pentoxifylline (PTX) is a methylxanthine phosphodiesterase IV inhibitor indicated for the treatment of peripheral occlusive venous diseases. Its mechanism is not completely understood, however, its anti-inflammatory activity was demonstrated in models transient brain ischemia, proposing that pentoxifylline may submit changes at central level. The aim of this study is investigate central effects of pentoxifylline in rats. **Methods:** Wistar rats were used, weighing between 170 and 200 g. The Ethics Committee and Animal Research (CEPA), UFC approved the work with the protocol number: 107/11. The animals were kept in collective cages, containing six animals each, which received water ad libitum diet, and are kept in a constant environment of 23 º C 25 º C, both in light and in the dark cycle of 12 hours. The animals were randomly divided into experimental groups of 6 rats each and named as follows: control (receiving vehicle), PTX 10, PTX 25 and PTX 50 (pentoxifylline 10 mg/kg, 25 mg/kg and 50 mg/kg respectively). Behavioral assessment in the open field test Open Field were used to assess the rate of exploitation. In the statistical analysis we used ANOVA, followed by pos test of Dunnett's, $p<0,05$. **Results:** The test Open Field gives an assessment of the animal's emotionality, locomotion and behavior, because of rising are linked mainly to motor coordination, while grooming behavior and defecation are associated with animal adaptation to the environment. Regarding the number of crossings can be observed that animals belonging to the higher dose (PTX50) had a higher exploratory capacity (43.80 ± 2.888) when compared to animals receiving vehicle (34.50 ± 1.118). Regarding the number of self-cleaning (grooming) and withdrawals (rearing) there was no statistical difference between groups. **Discussion:** In the open field test Open Field can be observed that pentoxifylline promotes important behavioral changes, since it promotes an increase in locomotor activity of the animals. These results should be evaluated by other behavioral tests that investigate better parameters and the pentoxifiline central hole. **Financial support**: Capes, CNPQ E FUNCAP.