03 Psychopharmacology

03.001 Cytochrome oxidase activity mapping in brain after physical and psychological stresses applied in unpredictable continuous mild stress (UCMS) protocols Schwerz JP[1,2], Homem KSC[1,2], Ramos AT[3,1], Dominguez CM[1], Soares MM[1], Scavone C[3], Troncone LRP[1,2] [1]IBu – Farmacologia, [2]IP-USP – Neurociências e Comportamento, [3]ICB-USP – Farmacologia

Previous studies developed in this lab described relevant differences among types of stressors and HPA axis response. All stressors induce remarkable ACTH secretion but antagonists of vasopressin 1b receptor can inhibit the ACTH response to physical stressors like ether vapor inhalation, while CRHR1 antagonists inhibit psychological stressors such as restraint. Mixed stressor such as forced swimming only had its effects blocked by concomitant use of both antagonists suggesting different modulations for physical and psychological stressors. Unpredictable Continuous Mild Stress (UCMS) is an important animal model of depression in which anhedonia is measured by sucrose preference. This model demands a long-term (2-3 weeks) exposure to a variety of stresses. Interestingly though, literature reports a significant rate of failure in this model. We hypothesize that different stress modalities, physical or psychological, may be more effective in inducing anhedonia, an aspect that has never been considered in these studies. Brain mapping of metabolic changes induced by stresses may offer clues to the understanding of the ongoing processes. Cytochrome c oxidase activity reflects long-term trends in energy demands allowing for an effective mapping of long-term changes in regional brain activity. We used 3 groups of 6 Wistar rats each that underwent UCMS protocols: a control non-stressed group (CON), a physical stress group (PHY) – cold exposure, box without bedding, box with water etc. and a psychological stress group (PSY) – restraint, crowded box, intruder in box, dominant in box, etc., for two weeks. All animals were then decapitated and brains were frozen at -80°C and later sliced at 30 µm in a cryostat. Slices were stained for cytochrome oxidase activity mapping by the DAB/cytochrome c standard method. Regions of interest were marked based on Watson&Paxinos rat brain atlas and measured by optical densitometry. Results showed that PHY stress induced statistically significant increases (1-way ANOVA) in: lateral periaquedutal gray (LPAG) - 6%; medial preoptic area (MPA) - 9%; anterior paraventricular hypothalamic nucleus (PaAP) - 8%; ventral paraventricular hypothalamic nucleus (PaV) - 3%; ventral bed nucleus of stria terminalis (STLV) - 10%; medial anterior bed nucleus of stria terminalis (STMA) - 6,5%; medial ventral bed nucleus of stria terminalis (STMV) - 11%. In PSY stresses, the areas were LPAG (4%), MPA (5%), PaV (3%), STLV (4%), STMA (6%) and STMV (4%). There were no significant differences in cytochrome c oxidase activity on the other areas examined (anterior and posterior basolateral amygdaloid nuclei, anterior and posterior basomedial amygdaloid nuclei, central amygdaloid nucleus, dorsomedial periaquedutal gray, substancia nigra compacta dorsal, lateral and reticular). A full comparative approach is envisaged as well as a complete discussion of the different roles of these brain areas in relation to stress and depression. **License number of ethics committee**: 1175/13 **Financial support**: FAPESP 2013/18897-7 & 2015/08098-5 CNPq 159503/2013-2 & 101288/2016-6

03.003 Respiratory and behavioral responses in the doxapram model of panic attacks in rat. Batista LA[1], Haibara AS[2], Lopes JB[3], Brianis R[3], Moreira FA[3] [1]UFMG – Farmacologia, [2]ICB-UFMG – Biologia e Fisiologia, [3]ICB-UFMG – Farmacologia
Introduction: Doxapram is a respiratory stimulant that induces panic attacks in humans. We aimed to characterize the cardiorespiratory, behavioral, and cellular effects of doxapram. We also evaluated alprazolam and the putative anxiolytic compound, URB597, an anandamide hydrolysis inhibitor, in the respiratory effect induced by doxapram. **Methods:** male Wistar rats received IV injections of doxapram and mean arterial pressure (MAP) and heart rate were measured simultaneously (veh, 5, 10, 20 mg/kg). After perfusion, brains were sliced for immunohistochemistry of c-Fos. The structures analysed were: dorsomedial, dorsolateral, lateral and ventrolateral PAG from three coronal planes that were averaged (rostral, intermediary, and caudal). Respiratory frequency induced by an IV injection of doxapram was analysed in a different group of rats. For the behavioral characterization we utilized the elevated T maze (ETM) and a conditioned place aversion protocol. Locomotor activity in an arena was measured (5 min) to exclude locomotion as a confounding factor for the ETM. One-Way ANOVA was used to analyze the cardiovascular parameters, the immunoreactive cells, the CPA paradigm, and the locomotion. 2-Way ANOVA followed by Bonferroni's test was used for the respiratory frequency and the ETM. **Results:** All doses of doxapram caused an increase in MAP and a bradycardia, $F(3,20)=20.79$, $p<0.01$ and $F(3,20)=19.60$, $p<0.01$. Regarding the c-Fos expression, there was a treatment effect for all the portions of the PAG: dmPAG: $F(3,59)=3.7$, $p<0.05$; dlPAG: $F(3,59)=3.5$, $p<0.05$; lPAG: $F(3,59)=5.6$, $p<0.01$; vlPAG: $F(3,59)=11$, $p<0.01$ (fig 8). 5 mg/kg of doxapram increased c-Fos protein expression only in the dmPAG, whereas 20 mg/kg increased c-Fos protein expression in all the other portions. In order to evaluate a possible pharmacological predictability of doxapram-induced tachypnea as an animal model of panic attack, we tested three doses of alprazolam (1, 2, and 4 mg/kg, ip route). There was a time effect and an interaction between time and treatment: interaction: $F(27,126)=2,41$, $p<0,01$; time: $F(9,126)=75,58$, $p<0,01$; treatment: [$F(3,126)=0,71$, ns]. Post-hoc analysis showed that 2 mg/kg and 4 mg/kg of alprazolam decreased the peak in RF. Three doses of URB597 (0.1, 0.3, and 1 mg/kg, ip route) were also tested. There was no interaction between factors. There was a time and a treatment effect. Interaction: $F(27,153)=0,56$, ns; time: $F(9,153)=49,50$, $p<0,0001$; treatment: $F(3,153)=4,05$, $p<0,05$. Post-hoc analysis revealed no effect of URB597. None of the doses induced a conditioned place aversion, $F(3,40)=2]$, $p=0.13$. All doses of doxapram increased inhibitory latency in the ETM, indicating an anxiogenic effect ($p<0.05$, Bonferroni's test), interaction $F(6,60)=3$; $p<0.05$. None of the doses altered basal locomotion, $F(3,21)=0.19$. **Conclusion:** this study showed that doxapram-induced tachypnea is a reliable tool for the study of panic attacks in rodents. Doxapram has an aversive property and recruits neurons from the PAG, a brain region related to defensive behaviors and possibly involved in the genesis of a panic attack. **Financial support**: CAPES, CNPq. **License number of ethics committee**: 259-2013 **Financial support**: CAPES, CNPq, FAPEMIG

03.004 Interaction between antidepressant doses of ketamine and the rewarding dose of ethanol: **Their effects on pro-apoptotic receptor P75 and anti-apoptotic receptor TRKB**. Contó MB, Camarini R USP – Farmacologia

Introduction: There is a high incidence of comorbidity between depression and alcoholism. Considering that ketamine has been demonstrating fast-acting and long-lasting antidepressant effect, it is important to investigate behavioral and toxicological interaction between these drugs. The conditioned place preference (CPP) is an animal model used to study the drugs' rewarding properties, as well as the potential of pharmacological treatment in altering such reward. Alterations in the expression of the neurotrophins and their receptors tyrosine kinase B (TrkB) and p75 seem to play an important role in neuroplasticity associated, respectively, to neuroprotection and pro-apoptotic events. **Aims:** Verify if the neuroplasticity produced by antidepressant doses of ketamine induces alteration in the ethanol rewarding effect evaluated by the CPP model. Investigate, in the hippocampus, possible differences in the protein expression of the receptors p75 and TrkB and possible differences in the expression of BDNF (agonist with high-affinity to TrkB and low-affinity to p75 receptor) and pro-BDNF (high-affinity agonist to p75 receptor). **Methods:** Naïve adult male Swiss mice, 75 days old, were housed in standard polycarbonate boxes, 5 mice/cage, food and water *ad libitum*. The protocol of CPP by ethanol (1.8 g/kg, i.p.) was divided in habituation (H1), conditioning (D2-D9) and test (D10). The antidepressant doses of ketamine were administered in the days D2, D4, D6 and D8, alternating with ethanol exposition, which was administered in the days D3, D5, D7 and D9 (always 24 hours after ketamine doses). In another experiment, mice were similarly treated with alternating doses of ketamine and ethanol, and twenty-four hours after the last injection, the animals were sacrificed, and their hippocampus dissected for realization of molecular experiments. This work was approved by our institution's Ethics Committee on Animal Research (Protocol 132/2016). **Results:** For the comparison of the behavioral parameter analyzed (Score) in the CPP test, the one-way ANOVA indicated a lack of significant differences among the groups ($p=0,92$). The one-way ANOVA indicated no differences among the groups for BDNF ($p=0,46$) and for pro-BDNF ($p=0,67$) levels. Concerning the expression of TrkB, the one-way ANOVA detected a difference among the groups ($p=0,04$) and the post hoc test of Newman-Keuls indicated a lower level of protein expression from the group Ethanol-Ketamine (50 mg/kg) compared to the group Saline-Saline ($p=0,04$). One-way ANOVA detected a significant difference among the groups in the levels of p75 receptor ($p=0,02$), and the Newman-Keuls test indicated a lower level of p75 receptor in the group Ethanol-Ketamine (50 mg/kg) compared to the group Saline-Ethanol ($p=0,014$). **Conclusion:** Our results demonstrated that the neuroplasticity induced by the antidepressant doses of ketamine do not affect ethanol rewarding effect measured in the CPP. An interaction between ethanol and the higher ketamine dose induced to a lower level of the TrkB receptor in the hippocampus, suggesting a pro-apoptotic effect. On the other hand, an interaction between ethanol and the higher dose of ketamine induced to a lower level of p75 receptor in the hippocampus, suggesting a protective effect against ethanol induced neurotoxicity. **Financial support**: Capes **License number of ethics committee**: 132/2016 **Financial support**: Capes

03.005 The effects of caffeine chronic treatment during adolescence in SHR and SLA16 rat strains. Granzotto N[1], Ramborger PAA[1], de Barros R[2], Izídio GS[2] [1]UFSC – Farmacologia, [2]UFSC – Biologia Celular e Molecular

Introduction: The locomotor hyperactivity is one of the most important endophenotypes of Attention-Deficit/Hyperactivity Disorder (ADHD). Although there are evidences explaining the neurobiological basis of this trait, it remains not fully understood in the literature. Currently, the most used animal model in ADHD research is the Spontaneously Hypertensive Rat (SHR). However, the translational value of SHR's studies has some limitations, and new models are necessary in order to better understanding of the ADHD and the locomotor hyperactivity neurobiology, as well as for the discovey of new therapeutic alternatives to treat it. We recently propose a congenic strain named SLA16, which is a strain derived from SHR and Lewis rats (part of chromosome 4 from Lewis rats was inserted in the SHR genetic background). Then, in experiment 1 we submitted SHR and SLA16 rats to open-field repeated protocol. Finally, in experiment 2, we chronically treated SHR and SLA16 rats with caffeine, during the adolescence, and tested them later in the open-field. **Methods:** In experiment 1, SHR and SLA16 male rats (10 weeks old) were submitted to the open-field (OF) repeated protocol (10 animals/strain). Animals were exposed to OF apparatus for 5 consecutive days, 5 min each day. In experiment 2, we first chronically treated both strains during the adolescence (postnatal days 24 to 45) with saline 0.9% or caffeine (2mg/Kg), via intraperitoneal, twice a day (8 animals/strain/treatment). After, we tested them in OF, at the end of treatment, and 30 days later. The analysis of the results was performed using a two-way ANOVA (experiment 1) or two-way ANOVA with repeated measures (experiment 2). When interaction between strain and treatment was detected, a *post-hoc* analysis was conducted with Duncan's test. All procedures were carried out in accordance with the guidelines of the local committee for Animal Care in Research (CEUA/UFSC) and had the valid permission PP00903. **Results:** In the first experiment, data showed that SLA16 have higher total locomotion than SHR rats ($F(1,18)=14.124$; $p=0.001$), and also a higher locomotion in the center of the arena ($F(1,18)=20.867$; $p=0.00001$). Interestingly, neither SLA16 nor SHR have habituated to OF, sustaining the locomotion scores along the protocol days ($F(1,18)=2.064$; $p=0.095$). The second experiment showed that caffeine chronic treatment diminished the total locomotion, at the end of the treatment, in OF in SLA16, but not in the SHR rats ($F(1,28)=4.21$; $p=0.049$). However, 30 days later no effect of strain ($F(1,28)=0.029$; $p=0.86$) or previous treatment ($F(1,28)=0.630$; $p=0.642$) were observed. **Conclusion:** Our data suggest that SLA16 rats are even more hyperactive than SHR. Furthermore, the caffeine chronic treatment during adolescence seems to ameliorate this endophenotype, diminishing the locomotor hyperactivity. But this effect seems to depend on the genotype and treatment regimen. **License number of ethics committee**: PP00903 **Financial support**: CAPES, CNPq

03.006 Study of ANKK1 (rs1800497) polymorphism of DRD2 gene in refractory and super refractory schizophrenia. Neri HFS[1], Rodrigues-Silva C[1], de Brito RB[1], Ghedini PC[1] [1]UFG – Farmacologia

Introduction: Schizophrenia is a chronic and severe psychiatric disorder which exhibits variability in response to many antipsychotic drugs. Clozapine (CLZ) is the gold standard treatment for refractory schizophrenia (TRS). However, approximately 30% of patients respond only partially to CLZ, constituting the individuals with super refractory schizophrenia (SRS). The genetic variations on dopamine D2 receptor (DRD2) are possible causes related to the impairment response to CLZ treatment. The most commonly studied DRD2 variant is a single-nucleotide polymorphism in *ANKK1* (rs1800497, Glu713Lys or 'Taq1A'). Carriers of the DRD2 TaqIA A1 allele is associated with reduced DRD2 gene expression and with a diminished dopaminergic activity in the central nervous system when compared to non-carriers or A2-carriers. The A1 allele has been associated with favorable responses to risperidone, aripiprazole and haloperidol, however, no studies evaluating the association of this variant with CLZ response are found. In the present investigation, the association of DRD2/ANNK1 polymorphism was evaluated in TRS and SRS patients. **Methodology:** A total of 109 patients were recruited, including 63 TRS and 46 SRS in CLZ treatment for at least 6 months. DNA was extracted from the venous blood of each patient and genotyping was performed using the PCR-RFLP technique. CLZ dose was collected and analyzed as recorded in his or her file. Statistical comparisons were performed using χ^2 and Fisher's test. Significance level considered was $p < 0.05$. All methodologies were approved by the Research Ethics Committees of the Health Department of the State of Goiás and Federal University of Goiás (protocols 1,537,538 and 1,483,734, respectively). **Results:** The A1 allelic frequency was 26% (TRS), 20% (SRS) and for A2 was 74% (TRS), 80% (SRS) ($p = 0.31$). The genotypic frequency for TRS was 5% (A1/A1); 43% (A1/A2) and 52% (A2/A2), and for SRS was 7% (A1/A1), 26% (A1/A2) and 67% (A2/A2) ($p=0.196$). The mean CLZ dose found for each different genotype for SRS was 500±0 (A1/A1); 641.6 ±99.6 (A1/A2) and 580.6±124.9 mg/day (A2/A2) ($p=0.124$), and for TRS was 533.3±51.6 (A1/A1); 483.3±184.3 (A1/A2) and 496.8±161.3 mg/day (A2/A2) ($p=0.774$). When compared the genotypes between SRS and TRS, the CLZ dose was higher in A1/A2 and A2/A2 genotypes of SRS ($p<0.0001$). However, these findings were not associated with DRD2/ANKK1 TaqIA polymorphism, because its allele and genotype frequencies were equally distributed between SRS and TRS. **Conclusion:** These previous results suggest that DRD2/ANKK1 TaqIA polymorphism not influences CLZ response in schizophrenic patients. **License number of ethics committee**: Research Ethics Committees of the Health Department of the State of Goiás and Federal University of Goiás (process 1,537,538 and 1,483,734, respectively). **Financial support**: CAPES; FAPEG; CNPq

03.007 Gender-related differences of hypercholesterolemia-induced memory deficits in a genetic model of familial hypercholesterolemia. Olescowicz G[1], Moreira E[2], de Bem AF[3], Prediger RDS[1] [1]UFSC – Farmacologia, [2]UFSC – Ciências Fisiológicas, [3]UFSC – Bioquímica

Introduction: Familial hypercholesterolemia is caused by mutations in the low-density lipoprotein receptor (LDLr) gene, causing loss of function of the LDLr and increased plasma cholesterol levels. Clinical studies indicate high incidence of mild cognitive impairment (MCI) and increased dementia predisposing in middle-aged familial hypercholesterolemia. Previous studies using low density lipoprotein receptor knockout (LDLr-/-) mice have demonstrated learning and memory impairments accompanied by neurochemical and neuromorphological changes. In this study we investigated putative gender-related differences in behavioral deficits of LDLr-/- mice in recognition memory and aversive memory tasks. **Methods:** Male and female C57B16 and LDLr-/- mice, a mouse model of familial hypercholesterolemia, aged 3-4 months were used. The experiments were performed after approval of the protocol by the Ethics Committee of the Institution (PP00948). To evaluate locomotor and memory parameters a behavioral analysis was performed. The short-term recognition and long-term contextual fear memories were addressed in the object recognition and fear conditioning tasks, respectively. The locomotor activity was addressed in the open field. The locomotor activity was addressed in the open field. Results were analyzed by one-way ANOVA followed by Newman-Keuls post hoc test, when appropriate (significant when $p<0.05$). **Results:** No significant locomotor differences were observed in males or females in the open field apparatus. In the object recognition task, it was observed a selective deficit of short-term recognition memory in male ($p<0.05$) LDLr-/- mice. On the other hand, in the fear conditioning tasks, both male ($p<0.05$) and female ($p<0.05$) LDLr-/- mice presented long-term contextual fear memory impairments. **Conclusion:** These findings reinforce the notion of the development learning and memory impairments in LDLr-/- mice, and provide the first evidence of the existence of gender-related differences in the cognitive impairments observed in this genetic model of familial hypercholesterolemia. **Acknowledgment:** Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) **License number of ethics committee**: PP00948

03.008 D1 Nucleus acumbens projection in context-induced reinstatement of alcohol seeking. Zaniboni CR, Palombo P, Yokowama TS, Moreira JF, Maeda RA, Cruz FC Unifesp-EPM – Farmacologia

Alcohol addiction is a world health problem associated with a higher rate of relapse during the treatment. Learned associations play a significant role in addiction and relapse. The nucleus accumbens direct and indirect pathway have been implicated in drugs of abuse reinforcing effects and reinstatement of drug-seeking. However, the precise mechanisms underlying these behaviors remain unclear. Here, we investigated the activation of substantia nigra reticulate (SNr) and ventral pallidum (VP) in context-induced relapse to alcohol-seeking. For this propose, male Long-Evans rats (n=25) were trained to self-administrate alcohol in context A and lever pressing was extinguished in a distinct context B. On the test day, context-induced reinstatement of alcohol seeking was tested in the context A. To investigate the activation of the striatal pathways we measured the neuronal activity marker Fos in the SNr and VP. Context-induced reinstatement of alcohol seeking was associated with decreased Fos expression in SNr neurons ($F_{(2,7)}$=0.90, p>0.05) and increased in VP ($F_{(2,13)}$= 5.97, p<0.05). Our results suggest that nucleus accumbens direct and indirect pathway may involve in context-induced reinstatement of alcohol seeking behavior. **License number of ethics committee**: 4094080317 **Financial support**: FAPESP Proc. Nº 2016/25894-2; Proc. Nº 2013/24986-2

03.009 Environmental enrichment promotes anxious-like behavior in mice submitted to a chronic unpredictable stress model. Silva NKGT, Costa GA, Almeida MG, Camarini R ICB-USP – Farmacologia

Introduction: Environmental enrichment (EE) consists of an experimental paradigm where animals are housed in an environment that allows social interaction, cognitive, motor and sensory stimulation at levels much greater than those that occur under standard laboratory conditions, which has been shown in literature as beneficial in several pathological situations, with reports of anxiolytic and antidepressant effects of stress. Thus, the hypothesis was posited that the EE could act as a promoter of resilience, since the daily exposure to mild stressors such as the presence of novelty and the constant exploration of the environment, as well as group coexistence in an environment complex that requires social interaction and response to different stimuli, would help the animal to deal better with later situations of more severe stress. In fact, several studies point to a protective effect of EE against acute stress situations such as maternal separation and restraint stress. However, the results for chronic stress are still controversial. In view of this, the aim of this study was to evaluate whether or not exposure to EE before and during the submission of mice to an model of chronic unpredictable stress (CUS) would be able to promote resilience in these animals, through the alteration of locomotor and anxiety-related behaviors. **Methods**. Sixty male Swiss mice (n = 15/group) were divided into four groups: 1) Non-Enriched and Non-Stressed (NE+NS); 2) Non-Enriched and Stressed (NE+ST); 3) Environmental Enrichment and Non-Stressed (EE+NS); 4) Environmental Enrichment and Stressed (EE+ST) (Protocol 120/2016). The enriched environment consisted of cages larger than the standard ones, endowed with objects with varied colors and textures, like exercise wheels, houses, plastic tubes, stairs and ramps; exchanged or rearranged 2 times a week in order to preserve the novelty in the environment, and the enrichment lasted 21 days plus the chronic unpredictable stress period (11 days), totaling 32 days. Chronic unpredictable stress included events such as forced swimming, light on during the dark cycle, lights off during the light cycle, isolation, deprivation of water and food, immobilization, wet bed, among others. The behavioral tests used were Open Field, Elevated Plus Maze and Light-Dark Box. **Results**. Our results indicated a reduction in the locomotor activity of EE+NS animals in the open field test and indicated a possible anxiogenic-like effect of EE in the elevated plus maze. In contrast, chronic unpredictable stress decreased anxious-like behavior and increased the exploratory activity of the animal. **Conclusion**. Our results indicate that although EE is described in the literature as anxiolytic in situations of acute stress, this data was not reproduced in our chronic unpredictable stress model. However, this correlation between enrichment and stress remains obscure, so further studies with different parameters and tests should be performed.

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03.010 Investigation of CB2 antagonist effects in the unpredictable chronic mild stress model of depression. Cardoso AR, Carvalho IN, Neves GA UFRJ – Farmacologia e Química Medicinal

Introduction: Major depression is a psychiatric disorder characterized by persistent sadness, anhedonia, change in appetite and sleep, anxiety, loss of energy, decreased concentration, among other symptoms that harm patients' daily life. Currently, this disorder reaches hundreds of millions of people around the world. Depression treatment includes psycho and drug therapy, however a considerable number of patients are unresponsive to these alternatives. Thus, new studies aiming a deeper understanding of depression neurobiological basis as well as looking for new therapeutic targets are needed. New studies have shown a possible link between the endocannabinoid system and the regulation of mood disorders and that type 2 cannabinoid receptors (CB2) could be involved. **Objective:** to investigate the effects of a CB2 antagonist in an animal model of depression in order to investigate its therapeutic potential. **Methods:** Swiss male adult mice are exposed to unpredictable chronic mild stress (UCMS) to develop a depressive-like phenotype (CEUA/CCS/UFRJ approval no. 131/16). The protocol involves exposing mice to 5 mild stressors per week during four to five weeks in a random schedule. The stressors include food deprivation, water deprivation, damp bedding, empty cage, cage tilt, white noise, strobe light, restrain and predator odor exposure. Anhedonia is one of the symptoms seen in people with depressive disorder and this phenotype can be assessed in animals through the sucrose preference (SP) test. After confirming the development of the anhedonic behavior, mice are divided in two groups: AM630 (CB2 antagonist, 1mg/kg/day i.p. for 12 days) and control (vehicle 0.1 mL/kg/day i.p.). After treatment, the following behavioral phenotypes are evaluated: SP, social approach and immobility behavior in the forced swimming test (FST). **Results:** Several SP protocols have been described, however there are still methodological issues do be addressed to optimize it. Initially we evaluated animals' preference for solution with different sucrose concentrations: 1.0% and 2.5%. The data obtained showed that, after one hour of free choice between water and sucrose, mice offered the 2.5% solution had higher consumption of sucrose (3.9 ± 0.1 g) when compared to those offered the 1% solution (3.0 ± 0.6 g). In addition, animals in the 2.5% group consumed more sucrose than water (1.8 ± 0.1 g) during the test, which indicates a preference for sucrose (68.8 ± 2.1% of total liquid consumed). This preference was slightly higher than that present by the 1.0% group (62.8 ± 4.3%). Furthermore, mice presented a high consumption of sucrose during the first 30 min of the test (2.5 ± 0.1 g, 71.8 ± 1.4% of preference), whereas in the last 30 min it decreased (1.4 ± 0.1 g, 62.2 ± 2.3 % of preference). **Conclusion:** In summary, using a 2.5% sucrose solution and an evaluation time of 30 min resulted in a more robust SP in mice. The optimized SP protocol evidenced the non-anhedonic profile of the animals before the UCMS. Currently a group of animals are being exposed to the UCMS protocol and treated with the CB2 antagonist. The behavioral assessments are underway. We expect to establish a robust animal model of depression, which will provide behavioral and biochemical phenotypes to allow the study of CB2 receptors as a potential target for depression treatment. **Acknowledgements:** CNPq, FAPERJ. **License number of ethics committee**: CEUA/CCS/UFRJ approval no. 131/16 **Financial support**: FAPERJ; CNPq

03.011 Investigation of the antidepressant-like mechanism of action from *Campomanesia xanthocarpa*. Anzolin GS[1], Petry F[2], Scapinello J[3], Ghettino JG[2], Oliveira JV[4], Magro JD[5], Muller LG[2] [1]Unochapecó – Farmacologia, [2]Unochapecó – Farmácia e Farmacologia, [3]Unochapecó – Farmacologia e Química, [4]Unochapecó – Gestão do Conhecimento, [5]Unochapecó – Engenharia Química

Introduction: Depression is the most disabling illness today, and the use of antidepressants causes debilitating adverse effects. Thus, the search for new therapies is necessary. In this scenario, the plant species Campomanesia xanthocarpa is included, which effects on the central nervous system have not yet been investigated. **Methodology**: The extract of C. xanthocarpa seeds was obtained through supercritical CO_2 e and its chemical composition determined using GC / MS. Three doses of the extract (30, 60 and 120 mg/kg, p.o.) were tested to standardize the lowest effective dose. Behavioral evaluations were performed using male Swiss mice, submitted to the tail suspension test (TSC), and the open field test. In order to evaluate the mechanism of action, also performed by TSC, antagonists of the monoaminergic pathways of the central nervous system were used before administration of the extract. Fluoxetine (30 mg/kg, p.o.) was used as positive control. The results (expressed as mean±S.E.M) were evaluated by one-way or two-way ANOVA post hoc Student-Newman-Keuls (Animal Research Ethical Committee-Unochapecó approval: 013/2017). **Results and Discussion:** The chemical analysis of the extract composition revealed the presence of terpenoids. In TSC, the dose of 60 mg/kg significantly ($p<0.01$) reduced the immobility time (s) (Sal=79.5±6.3; Extract 30=90.6±2.4; Extract 60=24±8.3; Extract 120=87.4±10.97; Fluoxetine=39.50±9.1; $F(4,24)=10.82$, $p<0.001$) of the animals . This dose did not alter the locomotor activity (number of crossings: Sal=380.4±10.17; Extract 60=376.2±16.2; Fluoxetine=287.8±30.4; $F(2,17)=7.01$, $p<0.001$) nor the vertical exploration of the mice in the open field test (number of rearings: Sal=93.2±9.9; Extract 60=86.8±6.92; Fluoxetine=61.5±25.88; $F(2,17)=1.21$, $p=0.33$), therefore discarding a stimulating effect of the extract. Fluoxetine significantly ($p<0.05$) decreased the number of crossings in the test. Regarding the investigation of the mechanism of action, sulpiride (dopaminergic D2 receptor antagonist) ($F_{pre\text{-}treatment}(1,22)=5.74$, $p<0.05$; $F_{treatment}(1,22)=0.34$, $p=0.56$; $F_{pre\text{-}treatment \times treatment}(1,22)=1.39$, $p=0.25$) prazosin ($F_{pre\text{-}treatment}(1,22)=20.89$, $p<0.001$; $F_{treatment}(1,22)=0.078$, $p=0.78$; $F_{pre\text{-}treatment \times treatment}(1,22)=1.71$, $p=0.21$) and yohimbine ($F_{pre\text{-}treatment}(1,23)=46.42$, $p<0.001$; $F_{treatment}(1,23)=0.19$, $p=0.66$; $F_{pre\text{-}treatment \times treatment}(1,23)=2.77$, $p=0.11$) (noradrenergic antagonists of α 1 and α 2 receptors, respectively) reversed the antidepressant-like action of the extract, thus affirming the involvement of dopaminergic and noradrenergic neurotransmission in the mechanism of action. The participation of serotonergic neurotransmission will be investigated in later tests. **Conclusion:** The extract of Campomanesia xanthocarpa presents antidepressant-like activity (at the dose of 60 mg/kg) mediated by dopaminergic and noradrenergic neurotransmission. **Keywords:** *Campomanesia xanthocarpa*, Depression, Mechanism of action. **License number of ethics committee**: 013-17 **Financial support**: Unochapeco / PIBIC / FAPE

03.012 Fludrocortisone impairs generalization of conditioned aversive memory in diabetic animals. Ribeiro TO[1], Stern CAJ[1], Andreatini R[1], Oliveira AR[3,2], Brandão ML[2], Zanoveli JM[1,2] [1]UFPR – Farmacologia, [2]USP – Neurociências e Comportamento, [3]UFSCar – Psicologia

Introduction: Diabetic (DBT) animals present an impaired extinction of aversive memories and an increased generalization of these same memories when compared to normoglycemic (NGL) animals. In addition, it is known that these animals have an increased level of circulating glucocorticoids, which is associated with an altered expression of the mineralocorticoids receptors (MR), responsible for Hypothalamus-Pituitary-Adrenal axis normal activity. Thus, we aimed to evaluate the effect of a single dose of the MR agonist, fludrocortisone (FLU), on the extinction and generalization of aversive memory of DBT animals. **Method**: Male Wistar rats (n=7-13) received one injection of streptozotocin (60mg/kg; ip) to induce diabetes, the NGL animals received the citrate buffer. After four weeks, animals were subjected to a conditioned contextual fear protocol to evaluate the freezing (index for fear response). The protocol is composed by: familiarization (context A, 3min, 28th day); contextual conditioning by 3 shocks of 1mA with 30s of interval before and after each shock (context A, 29th day); extinction training (context A, 15min, 30th day); extinction test (context A, 3min, 31st day); and generalization test (context B, 3min, 32nd day). The animals were injected with FLU (0; 5; 10 mg/kg, ip.), 20min before the extinction training (30th). As statistical analyses, except for the extinction training results, NGL group was compared to the non-treated DBT group using the students' T test; this last group was then compared to the treated DBT groups using One-way ANOVA and Newman-Keuls method as *post hoc*. For the extinction training, the NGL and non-treatead DBT group were compared using the Repeated Measures T-test, the later was then compared to the treated DBT groups using Repeated Measures One-way ANOVA and Newman-Keuls method as *post hoc*. Procedures were approved by the UFPR's Committee for the Ethical Use of Animals (#1073). **Results:** When compared to the NGL, DBT animals presented greater freezing response during extinction training and during extinction test associated with a generalization of aversive memory ($p<0.05$), suggesting an overconsolidation of these aversive memories. The treatment with FLU (5, 10mg/kg) did not change the increased freezing response during extinction training and during extinction test ($p<0.05$). However, treated-DBT animals (FLU, 5, 10mg/kg) showed a reduced freezing response in the generalization test ($P<0.05$). **Conclusion:** Our results suggest that MR agonist seems to induce a beneficial effect on aversive memory of DBT animals by impairing the generalization of conditioned aversive memory of DBT animals. **Acknowledgements:** We thank CAPES for the **Financial support**. **License number of ethics committee**: Aprovado pela Comissão de Ética no Uso de Animais, número 1073 **Financial support**: CAPES