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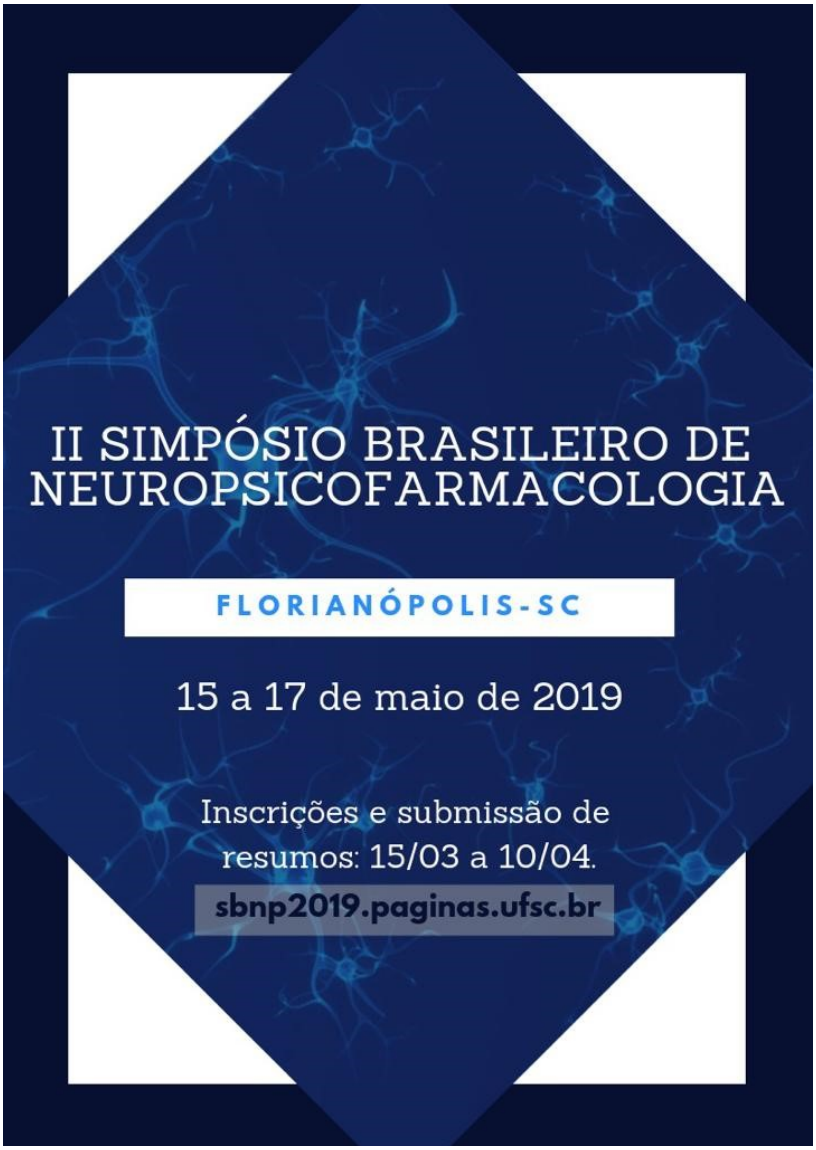
ABSTRACTS



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Poster

Role of nitric oxide in the acquisition of olfactory aversive conditioning induced by N-methyl-d-aspartate infusion into the periaqueductal gray matter

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Background: The role of nitric oxide (NO) in the immediate defensive responses (DR) elicited by stimulation of the periaqueductal gray matter (PAG) has been studied under different paradigms, and despite the years of investigation, its role in the acquisition of aversive conditioning has not yet been addressed. During the DR induced by N-methyl-D-aspartate (NMDA) microinjection into the PAG, an increased NO level occurs activating a biochemical cascade that regulates the glutamatergic neurotransmission.

Objectives: To better understand the importance of NO in aversive learning protocols, this study addressed to the role of the nitrergic signaling pathway in an olfactory aversive conditioning (OAC) paradigm using the chemical stimulation of the PAG by NMDA.

Methods: Male Wistar rats (260-360 grams) with implanted cannulas placed in the PAG were used. Ten days after neurosurgical recovery, the rats were exposed to the OAC protocol, consisting of two phases, 1) acquisition phase (familiarization and conditioning day) in the conditioning chamber, and 2) expression phase (familiarization and test day) in the odor box. To evaluate the influence of NO in the immediate DR and in the OAC acquisition, during the conditioning session, a nitric oxide synthase inhibitor, 7-Nitroindazole (7NI) 40 and 100 nmol, or the NO scavenger, Carboxy-PTIO (c-PTIO) 1 and 2 nmol was infused (0.2 µl) into the PAG 10 min before the microinjection of NMDA 50 pmol that was used as an aversive stimulus paired with amylacetate odor (protocol approved by the CEUA N° 4301200818).

Results: The results demonstrated that both, 7NI and c-PTIO, were able to decrease the DR induced by microinjection of NMDA 50 pmol on the conditioning day, interfering also with further OAC acquisition and expression measured on the test day.

Conclusion: Considering that inhibition of NO synthesis as well as its sequestration decreased defensive behaviors and impair acquisition of OAC, we conclude that NO not only play an important role during the DR in the OAC, since it shows an active participation in the learning of this paradigm.

Poster

Resveratrol Prevents Edema Formation through the Regulation of SUR1 Expression in Brain Micro-Vascular Endothelial Cells

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Background: Cerebral edema is a clinical problem that frequently accompanies stroke. Edema formation is a prognosis of functional deterioration and represents the main cause of death in patients in which ischemia involve large portions of a hemisphere (1). The SUR1-NCCa-ATP ion channel is overexpressed in the initial phase of edema formation, allowing the massive internalization of Na2+ and water within the cerebral micro-vascular endothelial cells of the blood brain barrier, causing alteration in its function (2). Expression of the Abcc8 gene encoding SUR1 depends on transcriptional factors that are sensitive to oxidative stress (3). Because large amounts of reactive oxygen species (ROS) are generated during cerebral ischemia, we hypothesized that antioxidant compounds might have the ability to regulate the expression of SUR1.

Objectives: Therefore, we evaluated the effect of resveratrol on SUR1 expression in brain micro-vascular endothelial cells using an in vitro model of cerebral ischemia.

Methods: The brain micro-vascular endothelial cell line of human origin HBEC-5i was subjected to oxygen and glucose deprivation (OGD) for 2 h, followed by different recovery times. Resveratrol was administered after OGD and a dose-response was achieved. ROS production was detected with etidine, SUR1 protein level was evaluated by Western blotting and immunofluorescence, cellular swelling was measured by cellular volume change, cellular viability was evaluated by an MTT assay, and necrotic cell death by LDH release. Furthermore, transcription factor activity was evaluated by EMSA assays and protein nuclear translocation by immunofluorescence.

Results: OGD increased ROS production and induced the expression of SUR1 (13.0 ± 5.2-fold) in the HBEC-5i cells from 6 h of recuperation, reaching maximum values after 24 h. This effect correlated with cellular swelling (5.2 ± 0.6 %) and necrotic cell death (2.2 ± 0.45-fold). Both cellular responses were prevented by resveratrol administration, with the maximum effect observed at 5 µM. Reduction of ROS by resveratrol was observed after 4 h. OGD increased binding activity of Sp, HIF-1α, and NF-κB. And inhibitors of these transcriptional factors decreases SUR1 expression.

Conclusion: Resveratrol prevented cellular edema formation through modulation of SUR1 gene expression. Thereby, our findings represent an advance

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in the description of the molecular mechanism of action of resveratrol in reducing cerebral edema.

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Poster

Evaluation Of Polygala paniculata Hydroalcoholic Extract Effect In Stroke Models In vitro and In Vivo

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Background: Stroke is one of the leading cause of death worldwide [1]. The resulting neuronal death triggers the main symptoms such as motor disabilities, vascular dementia and depression, affecting individuals during their productive life. The approved treatment for stroke is the Alteplase, an anti-trombolitic drug with a narrow therapeutic window with multiple side effects. Medicinal plants are seeing as a source of compounds with biological activity, which can minimize damage to the CNS. Polygala paniculata has already shown antitumoral, antinociceptive and neuroprotective properties [2-5].

Objectives: Evaluate Polygala paniculata hydroalcoholic extract effect in stroke models in vitro and in vivo

Methods: Cortical neurons in culture were exposed to oxygen and glucose deprivation (OGD). In summary, conditioned culture medium was removed from the cultures derived from ED ~14.5 mice and replaced by OGD buffer with different concentrations of PpHE (10-100 □g/ml) and kept for 90 minutes in a hypoxic chamber (0.5% O2, 37 ºC and 5% CO2). In parallel, 4-well plates were left at normal cell culture conditions for the same time with OGD buffer supplemented with 25 mM glucose. To evaluate cell survival, apoptosis levels were measured via Hoechst staining. Additionally, global ischemia was induced in mice by bilateral common carotid arteries occlusion (BCCAo). Mice were treated with PpHE 1 mg/kg, via oral, twice a day, for 2 days. Maximal grip strength was assessed before surgical procedures and 48h later. After that, animals were sacrificed, brains were removed and stained with 2,3,5-triphenyltetrazolium chloride. Damaged areas were quantified.

Results: Treatment of 4-well plates with PpHE (10-100 □g/ml) did not affect the cell survival of cortical neurons [F(3,10)= 0,5003; p= 0,6904]. Under OGD conditions, cell survival of cortical neurons treated with PpHE (100 □g/ml) was significantly higher than untreated neurons [F(3,12)= 11,13; p= 0,0009]. Related to animal model, mice have a decrease in maximal grip strength after BCCAo compared to baseline assessment [F(1,13)=102,2; p<0,0001]. This decrease attributable to BCCA was 35±7% (control group, n=8). PpHE treatment resulted in a reduction of 10±6% in grip force; the reduction was significantly lower [F(1,13) = 31,02, p<0,0001) as compared to the control group. Animals treated with PpHE had a significantly lower infarct area (27.12±1.533%, n=4) compared with control group (40.93±5.414%, n=5) (t=2,197,df=7, p=0.0320).

Conclusion: PpHE treatment can prevent apoptosis in cortical neurons under OGD conditions, indicating neuroprotective effect of this extract in vitro. Also, PpHE treatment can prevent decreasing of grip force and infarcted area in mice after BCCAo.

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Poster

Neuronal Ensembles Molecular Adaptations and Incubation of Cocaine Craving

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Background: Relapse is the major challenge in cocaine addiction treatment and can be caused by the exposure to environmental stimuli previously associated with drug use, a process that involves associative learning [1]. As extensively demonstrated, associative learning is encoded by a small specific neuronal group sparsely distributed throughout the brain, known as neuronal ensembles [2]. Even though addiction be recognized as a neuroplasticity disorder, most of these molecular plasticities are still unknown. Additionally, given the role of associative learning and neuronal ensembles, molecular adaptations relevant for drug relapse should be sought in these group of neurons and not in random neuronal populations [2-3]. It was demonstrated that some of the addiction-related plasticities are modified during the abstinence period and these modifications appear to be pivotal for the increase of the cue-induced cocaine craving [1]. This phenomenon is termed incubation of drug craving.

Objectives: Our study aims to investigate molecular adaptations related to the incubation of cocaine craving in neuronal ensembles selectively activated by cocaine-related cues.

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Methods: Jugular vein of male Wistar rats was catheterized for cocaine self-administration. Next, rats were trained to self-administer cocaine 6h/day (extended access) or 1h/day (restricted access), for 12 days in a context specific. All infusions were paired with cues. Then, we assessed relapse to cocaine seeking after 1 and 30 abstinence days (Animal Research Ethical Committee number: 4183030918).

Results: Extended access produced a higher cocaine intake normalized for the first hour of consumption and induced a more prominent escalation on cocaine consumption, mimicking the transition between occasional use to the abusive use. Further, only extend access rats presented incubation of cocaine craving behavior.

Conclusion: Our data indicate that extended access is a better protocol to induce incubation of cocaine craving when compared with restricted access. In future studies, we will investigate the neuronal ensembles molecular plasticities related to incubation of cocaine craving.

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Poster

The Monoamine Stabilizer, OSU-6162, Reduces Cocaine-Induced Hyperlocomotion and Acquisition of Conditioned Place Preference in Mice

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Background: Despite cocaine addiction being considered a serious brain disorder, there are few available treatment options [1]. One possibility is the use of antipsychotics modulating dopaminergic and serotonergic systems, since cocaine reward has been linked to both neurotransmitters [2].

Objectives: Thus, the aim of this study was test the hypothesis that OSU-6162, a monoaminergic stabilizer [3], inhibits cocaine-induced hyperlocomotion and conditioned place preference (CPP), which model the hyperactivity and the contextual memory underlying drug seeking, respectively

Methods: In hyperlocomotion experiment, the distance travelled was recorded in male Swiss mice in a circular arena. After a 10-min habituation, the mice received cocaine (15 mg/kg, intraperitonealy, ip) and were immediately submitted to the same arena for a 10-min test period. OSU-6162 (3, 10, and 30 mg/kg, ip) was injected 20 min before habituation. The CPP was divided in three phases: pre-test (day 1), in which male swiss mice could explore the entire apparatus; conditioning (day 2 to 7), in which cocaine was paired with one of two chambers; and test (day 8), when mice were tested for the expression of cocaine-induced CPP. The effects of OSU-6162 (3 and 10 mg/kg, ip) on acquisition and expression of reward memory were investigated injecting it in the conditioning or test phase, respectively. The preference score was defined as the time spent in the drug-paired chamber on day 8 minus on day 1 (Animal Research Ethical Committee of UFMG approval: 55/2016). The data were analyzed by ANOVA followed by the Tukey's test, with p-value set at 0.05.

Results: In hyperlocomotion experiment, there was no difference in distance travelled among all groups in habituation. In test phase, cocaine induced an increase in total distance travelled, which was partially prevented by the lowest dose of OSU-6162 (3 mg/kg) ($F(4,34)=8,896$, $p<0.05$). In CPP, mice from cocaine group, but not from OSU-6162 group, presented a higher preference score compared to control group. OSU-6162 (3 mg/kg) prevented acquisition, but not expression, of cocaine-induced CPP ($F(3,50)=11,54$, $p<0.01$).

Conclusion: OSU-6162 prevented both hyperlocomotion and acquisition of reward memory induced by cocaine, at doses that did not affect basal locomotion or place preference per se. These results corroborate with the potential of OSU-6162 as a candidate for treatment of cocaine addiction. However, more studies are warranted to extend these finds. FINANTIAL SUPPORT: FAPEMIG/CNPq.

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Poster

EVALUATION OF THE DOPAMINERGIC SYSTEM IN ZEBRAFISH SUBMITTED TO THE EXPOSURE MODEL TO ALCOHOLIC BINGE

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Background: Binge drinking is a type of drinking pattern characterized by ingestion of high doses of alcohol in a short period leading to many negatives effects to individuals and society. The dopaminergic reward pathway has been targeted by psychoactive substances, such as alcohol, stimulating the release of dopamine. Zebrafish has been used as an animal model in order to mimic binge drinking and study the effects of alcohol on the vertebrate brain due to a number of advantages of this species and its similarity to humans at neural level.

Objectives: Binge drinking is a type of drinking pattern characterized by ingestion of high doses of alcohol in a short period leading to many negatives effects to individuals and society. The dopaminergic reward pathway has been targeted by psychoactive substances,

Methods: During the experimental phase, the animals were exposed to ethanol (1.4% v/v) for 30 minutes, once a week for three consecutive weeks. WB-I (analyzed immediately after the last exposure), WB-2 (after 2 days) and WB-9 (after nine days) were divided according to the time of analyses after the third and last exposure to ethanol. The control group was also manipulated to groups WB-I, WB-2 and WB-9 exposed in an aquarium of the same dimensions. After this period, the brains were dissected and dopamine uptake was evaluated using 0.035 Ci/mL, corresponding to 10 nM L[3H] dopamine and 0.75 nM unlabeled dopamine in the samples. The MAO activity was performed by fluorescence method, using quinuramine as a non-selective substrate for MAO-A and MAO-B. The HPLC method, proposed by De Benedetto et al. (2014) was adapted to assess total dopamine levels. For the analysis, the injection volume of the samples was 20 µL at a temperature of 35°C. Detection was performed by fluorescence (excitation at 279 nm and emission at 320 nm). The peaks were identified and quantified by comparing their retention time in the sample solution to that of the standard solution, by means of a calibration curve.

Results: The WB-I and WB-2 groups showed a significant increase in the activity of the dopamine transporters compared to the control group. In contrast, the WB-2 and WB-9 groups showed a decrease in activity when compared to the MAO enzyme. At total brain dopamine levels, groups WB-2 and WB-9 showed an increase when compared to the control group.

Conclusion: These findings lead to the conclusion that dopaminergic parameters are still susceptible after two and nine days from the last alcoholic exposure in this experimental model, resulting in a modulatory event in this neurotransmission pathway. These results create new perspectives for behavioral studies on drug addiction.

Every procedure concerning the use of animals was approved by the Ethics Committee on Animal Use (CEUA) of the Universidade do Extremo Sul Catarinense under protocol No. 010/2017-2.

Poster

Cb1 Receptor Antagonism Prevents Hyperlocomotion Induced By The Dopamine Transporter Inhibitor Gbr12909

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Background: Bipolar disorder is featured by occurrence of mania and depression episodes and the neurobiological mechanisms remain poorly understood. The inhibition of dopamine transporter by GBR12909 was recently proposed as animal model of mania. The endocannabinoid system modulates dopaminergic neurotransmission

Objectives: We tested the hypothesis that CB1 receptor antagonism prevents hyperlocomotion induced by GBR12909.

Methods: C57Bl6 male mice (25–30 g; 10/group) were pretreated with vehicle, lithium carbonate (50 mg/Kg) or the CB1 receptor antagonist AM251 (0,1; 0,3; 1 and 3 mg/Kg) and 20 min later they received injections of saline or GBR12909 (15 mg/Kg). Locomotion was analyzed immediately after the second injection by Any-maze Software. The data were analyzed by ANOVA followed by the Bonferroni test and pvalue was set at 0.05.

Results: GBR12909 administration increased locomotion and positive control Lithium and the highest dose of AM251 inhibited this effect.

Conclusion: GBR12909 administration seems to be a useful model of mania-like behavior, since it mimics some changes observed in patients undergoing a mania state, moreover, CB1 antagonist can inhibit the effect of GBR12909.

Oral

The Good, The Bad And The New About The Effects Of General Anesthetics In Behavioral Pharmacology

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Background: The use of general anesthetics to perform surgeries in psychopharmacological studies is a fundamental approach to assure health and animal welfare. However, the long-term antidepressant and anxiolytic-like effects induced by general anesthetics such as ketamine [1, 2] and isoflurane [3] raise the concern about the potential bias of their use as anesthetics in surgeries that precede psychopharmacological assessment.

Objectives: Thus, our group recently provided some evidence that tribromoethanol and chloral hydrate seem to be improper anesthetics for surgeries that precede behavioral analysis in the elevated plus-maze (EPM), whereas isoflurane and thiopental may be suitable for

Methods: On the other hand, the long-term antidepressant effects of ketamine and isoflurane in clinical studies and practice also pointed to the potential of general anesthetics as drugs to treat other psychiatric diseases.

Results: A comprehensive review of the literature showed that there is a widespread discordance among pre-clinical studies addressing anxiety and panic-related effects of ketamine. Regarding the obsessive-compulsive disorder, we and other groups have also been investigating the effects of some general anesthetics on the marble burying behavior (MBB). We found that a single administration of a sub-anesthetic dose of S-ketamine reduces MBB in mice and that this effect involves the ventromedial orbitofrontal cortex and AMPA receptors [5], as well as depends on sex of the animals. On the other hand, exposure to sub-anesthetic and anesthetic concentrations of the inhalational anaesthetics isoflurane and sevoflurane does not affect MBB.

Conclusion: The current evidence suggests that some general anesthetics may be a potential bias in behavioral studies. Some recent findings also strength the potential of ketamine to treat different psychiatric disorders.

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Poster

Neurochemical And Behavioral Changes After Weekly-Binge Exposure To Ethanol In Zebrafish

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Background: Alcohol is a substance capable of causing several tissue and organ's damage, highlighting its harmful effects on the brain by modulating many mechanisms and pathways, such as changes in neurotransmission systems, activation of pro-oxidant pathways, and induction pro-inflammatory system. Among the patterns of consumption of alcoholic beverages, a standard stands out, the binge drinking. This behavior of consumption is characterized by the ingestion of high doses of alcohol in a single episode, followed by a period without the ingestion of alcoholic beverages. Because it is a behavior of little consumption studied, the compression of the effects of ethanol on the brain in this pattern of consumption is of great importance.

Objectives: In this context, the purpose of the present study was to evaluate the effects of a model that mimics the binge drinking (weekly-binge) on cholinergic signaling, oxidative and inflammatory responses in zebrafish brain. We also evaluated locomotor and explo

Methods: The model consisted of three exposures to ethanol (1.4% v / v) for 30 minutes. The groups were divided according to the time of analysis after the third and last exposure to ethanol: WB-I (analyzed immediately after the last exposure), WB-2 (after 2 days) and WB-9 (after 9 days). Part of the animals in each group underwent euthanasia and had the whole brain dissected for biochemical analyzes, the remainder being used in the behavioral test. To verify oxidative stress, the levels of thiobarbituric acid reactive species (TBA-RS), dichlorofluorescein oxidation (DCFH) and the activity of the enzymes superoxide dismutase (SOD) and catalase (CAT) were evaluated. Parameters related to inflammatory events were evaluated by analyzing the expression of genes related to cytokines IL-1β, IL-10 and TNF-α. From the cholinergic system, the activities of the enzymes choline acetyltransferase (ChAT) and acetylcholinesterase (AChE) were evaluated. In the behavioral analysis, the Novel tank test was used.

Results: When analyzing the parameters of oxidative stress, there was an increase in TBA-RS levels and an increase in the oxidation of DCFH in the WB-I group. Regarding the antioxidant enzymes, changes were observed in the WB-2 and WB-9 groups, characterized by the decrease of CAT in these groups. The weekly-binge was not able to promote alterations of the gene expression for IL-1β, IL-10 and TNF-α. On the cholinergic system, the exposure model could increase the ChAT activity in the WB-I group while in the WB-9 group a decrease in activity was apparent. AChE activity decreased in the WB-2 and WB-9 groups. In

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the Novel tank behavioral test, the weekly-binge could promote an anxiolytic effect in the WB-I and WB-2 groups by altering the exploratory behavior of the animals.

Conclusion: Considering the results obtained in the parameters of oxidative stress and cholinergic system, we can suggest that pro-oxidant pathways can alter cholinergic transmission, as well as the behavioral alteration may be a response of the alteration in this neurotransmission system. These results contribute to a better understanding of the pathological mechanisms involved in the intermittent consumption of ethanol.

Poster

Maternal separation stress influences alcohol consumption in the adulthood.

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Background: Alcohol is a drug of abuse commonly used worldwide. Addiction to ethanol affects millions of people nationwide. Many different factors play into the causes of alcohol addiction. For instance, early life stress is considered an important risk factor for alcohol addiction However, the neurobiological mechanisms underlying stress-induced augmentation of alcohol taking and seeking are not fully understood. In rodents, the maternal separation model has been considered very predictive to demonstrate the effects of early stress exposure on ethanol consumption.

Objectives: This study aimed to evaluate the neurobiological and behavioral influence of maternal separation on alcohol consumption in mice.

Methods: From postnatal day (PND) 1 to 14, C57BL/6J pups were submitted to maternal separation stress protocol daily, for 180 min. The control group was left undisturbed, only handled during cage cleaning. On PND 45, female and male mice (n=15) were exposed, in their home cages to bottles containing alcohol 20% (w/v) for 4h daily during the dark cycle (DID) of light during 3 weeks. The DID was followed by alcohol self-administration in operant chambers. Following the acquisition phase, the breakpoint was determined during 2 hours sessions. Then mice were allowed 4 h of free access to alcohol 20% (binge consumption).

Results: In the second week of consuming, female mice which were submitted to maternal separation consumed more alcohol than those which were left undisturbed. On the first week, male mice subjected to maternal separation consumed more alcohol than their control group. No significant differences were observed among the groups in the breakpoint parameters. In the binge protocol, the female maternal separation group drank more alcohol than the control ones. On the other hand, separated male mice drank less than those mice which were left undisturbed.

Conclusion: Maternal separation stress may influence alcohol consumption in adulthood.

Poster

A protocol for the systematic review and meta-analysis of the evidence linking hippocampal neurogenesis to the effects of antidepressants on mood and behavior

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Background: Findings in rodents have associated synaptic losses, decreased function, and formation of new neurons in the regions of prefrontal cortex and hippocampus with depression [1]. According to the current theories, a psychiatric disorder-bearing organism would present one or more neurochemical deficiencies that would be corrected by chronic treatment with antidepressants [2]. In this sense, monoaminergic theory, neuroplasticity and hippocampal neurogenesis could be related to the underlying effect of antidepressants [3]. The neurogenic theory argues that the reduction of hippocampal neurogenesis occurs through stress would be corrected by chronic treatment with antidepressants [4].

Objectives: Here, we present a protocol to systematically and quantitatively evaluate the relationship between hippocampal neurogenesis and the effects of antidepressant drugs on mood or behavior.

Methods: The study methodology is anchored in the Systematic Review and Meta-Analysis (RSMA) protocol. Such protocol [5] is available on the https://osf.io/s6ady/ link in the English version, which enables extensive data analysis with robustness and accuracy and data statistics later. Search strategies, such as keywords, databases, etc, are thought a priori; identification and storage of the selected studies according to the inclusion and exclusion criteria present in the RSMA protocol and extraction of data that will be tabulated for the construction of the meta-analysis. The meta-analysis will be done using measure of effect, which will include mean difference, standardized mean and risk ratio; statistical analysis model or random or fixed effects model; heterogeneity

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assessment models; subgroup analysis and sensitivity; besides a correction method for multiple tests, multiple use of the control group and evaluation of publication bias.

Results: It is hoped to obtain the effect sizes of antidepressants on different markers of hippocampal neurogenesis (e.g. BrdU, Ki-67, DCX), the correlation between hippocampal neurogenesis and behavioral effects of antidepressants in rodents. Moreover, it expect to estimate accurately the influence of experimental settings− such as species interference, age, sex, cell marker, time of drug administration, etc., − on the relation between hippocampal neurogenesis and behavioral effects of antidepressants.

Conclusion: Due to the abundance of data and the accumulation of information that require more robust synthesis strategies than in the past, the expected results are the systematization of information that will support future projects on the neurogenic theory for antidepressants.

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Poster

Selective inhibition of phosphodiesterase 4 by roflumilast prevents memory impairments and activates anti-inflammatory mechanisms in the hippocampus of rats subjected to transient global cerebral ischemia.

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Background: Background: Inclusion of internal validity criteria such as the use of animals of different ages, both sexes, presence of comorbidities and also the use of different animals models, have been strongly encouraged by experts in order to increase the relevance of preclinical studies in ischemic brain diseases. Recently, we have shown that roflumilast, a selective phosphodiesterase 4 inhibitor (PDE4-I), improved memory deficits induced by chronic cerebral hypoperfusion (CCH) in aged rats. However, there are no reports of the effects of roflumilast in other brain ischemia models.

Objectives: Objetive: To evaluate the effects of roflumilast in the transient global cerebral ischemia (TGCI), an experimental model that an immediate and severe outcome of reversible cardiac arrest in rats.

Methods: Methods: Wistar rats underwent 4-vessel occlusion model of TGCI (Ethics Committee approval 5529100517). Roflumilast (0.003 or 0.01 mg/Kg) or vehicle was administered during 21 days after TGCI. On day 7, 14 and 21 the rats were tested in the aversive radial maze (AvRM), to evaluated retrograde memory. The parameters analyzed were: latency time and the number of reference and operational erros. After behavioral testing, the rat brains were removed and the hippocampus were examined for neuroplasticity markers including doublecortin (DCX) and phospho-cyclic AMP-response element binding protein (CREB) and inflammation markers such as the ionized calcium binding adaptor molecule 1(Iba-1), glial fibrillary acidic protein (GFAP), Arginase-1 (Arg-1), the cytokines IL-10 and IL-4 and TNF.

Results: Results: TGCI caused persistent retrograde amnesia and elevation in the hippocampal levels of Iba-1 ($2 = 10.59$, $p=0.01$) and GFAP ($2 = 12.84$, $p=0.005$) 21 days after the injury. Ischemic animals treated with roflumilast (0.003 and 0.01 mg/Kg) presented a decrease in the latency time ($F3,120=21.14$, $p<0.0001$), number of reference errors ($F3,120=17.34$, $p<0.0001$) and operational errors ($F3,120=13.68$, $p<0.0001$) in the AvRM compared to controls, which suggests functional recovery. Roflumilast increased the levels of phosphoCREB in the CA1 hippocampal subfield ($2 = 21.51$, $p<0.0001$) and the number of DCX-positive neurons ($2 = 120.74$, $p<0.0001$) in the subgranular zone of dentate gyrus. Roflumilast did not change the levels of NeuN in the hippocampus of ischemic rats when compared to controls ($2 = 15.95$, $p=0.001$), indicating that this treatment did not protect the neurons from ischemia. The highest dose of roflumilast (0.01 mg/Kg) increased levels of Arginase-1 ($2 = 8.36$, $p=0.04$) and IL-10 ($2 = 8.78$, $p=0.03$) in the hippocampus. There were no changes in the hippocampal levels of IL-4 or TNF ($p>0.05$).

Conclusion: Conclusions: Roflumilast prevented memory impairments, increased CREB phospholiration and hippocampal neurogenesis, but not protect the neuronal loss in the hippocampus induced by TGCI. The protective effects of roflumilast in TGCI may involve stimulation of hippocampal neurogenesis and activation of anti-inflammatory mechanisms.

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Oral

Environmental and pharmacological influences on ethanol-related behaviors

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Background: Our laboratory has focused most of its research on how environmental enrichment (EE) and oxytocin may influence ethanol-elicited behaviors. Our studies showed that EE prevented and reversed ethanol-induced behavioral sensitization, decreased ethanol intake after an acute exposure to restraint stress, but increased ethanol-induced conditioned place preference (CPP) in both adolescent and adult mice. This latter effect seems to be oxytocinergic system-dependent.

Objectives: This study aims to evaluate the effects of environmental enrichment (EE) or oxytocin (OT) on ethanol-induced rewarding effects, social stimuli, and hedonic stimuli, to study the effects of EE on the gene expression of oxytocin and vasopressin receptors in

Methods: Enriched or control mice were tested for their social or ethanol preference,by conditioned place preference and for ethanol intake. The Crawley test was used to measure social interaction and food enticing to evaluate motivation in these two groups. We evaluated the effects of EE on PLC activity in the presence of OT in the striatum and gene expression of V1a, V1b, VP, OTR and OT in the hypothalamus and striatum. Because of the similarities between OT and vasopressin (VP), we performed analysis of the cross response between OT and VP and their V1a and OTR receptors, respectively, on the release of Ca2 +

Results: The rewarding effects of social stimulus were not able to reverse the increase in ethanol preference in enriched animals, despite the increase in social interaction promoted by this environment. This potentiating effect of EE on ethanol reward appears to be an ethanol-directed effect, since in the face of high hedonic food, EE attenuated searching behavior. Interestingly, treatment with carbetocin exhibited a response pattern similar to EE in preference to ethanol vs. social. Regarding ethanol intake, both EE and oxytocin decreased ethanol intake before exposure to stress. The results of gene expression indicated no differences between OT and VP receptor mRNA concentrations between control and enriched animals, although EE mice had a higher concentration of OT in the hypothalamus and VP in striatum. Finally, cross-interaction between the OT and VP systems, in vitro, was also shown through the Ca 2+ release test.

Conclusion: EE and oxytocin promotes an increase in the conditioned preference to ethanol, even in the face of social reward, although both strategies have decreased ethanol intake. This occurs despite the positive influence of EE in social behaviors (interaction and dominance) and decrease in motivation for searching palatable foods. High OT in hypothalamus may have some influence on these effects.

Oral

Involvement of cannabinoids on the reconsolidation of contextual drug- associated memories.

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One of the most challenging aspects of drug addiction is the craving and relapse. The persistence of drug-seeking and drug-taking behaviors suggests that drug-associated learning and memory processes contribute to this relapse. Memory reconsolidation, the process by which memories are restabilized after retrieval, may have relevance to addiction both potential therapy and as a mechanism for maintaining and strengthening of cue-related memories over time. The endocannabinoid system plays important roles in a variety of function in the mammalian brain, including the regulation of drug-reward and memory. Preclinical studies demonstrate that cannabinoid receptors modulate addictive behaviors. Further, cannabidiol, a non-psychotomimetic constituent of Cannabis also impairs drug-related behaviors, including the reconsolidation of contextual associative drug-memories in rats. The current presentation provides important implication that cannabinoids have on the reward memory and highlights the view that reconsolidation disruption mediated by pharmacological modulation of endocanabinoid may be a therapeutic value to disrupting the long-lasting memories that can trigger relapse.

Poster

Cannabidiol as a potential therapeutic agent in the treatment of depression and anxiety associated with diabetes

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Background: The association of diabetes with depression/anxiety has been increasing over the years, worsening patients' quality of life and increasing morbidity and mortality. It becomes urgent to treat depression/anxiety with a drug that also improves the diabetic condition. In this sense, cannabidiol (CBD),

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one of the most abundant non-psychotomimetic compounds present in the Cannabis sativa plant, has been identified as a possible therapeutic agent in the treatment of depression, anxiety and diabetes.

Objectives: Thus, the purpose of the study was to investigate the effect of repeated treatment with CBD (2 weeks) on behavioral responses of anxiety-like and depression-like in diabetic animals and a possible involvement of neurotransmitters such as serotonin (5-HT),

Methods: Diabetes was induced in male Wistar rats by the injection of streptozotocin (60 mg/kg, i.p). Two weeks later, repeated treatment (14 days) with CBD (0, 3, 10 and 30 mg / kg i.p.), imipramine (15 mg/kg, i.p.) as a positive control and/or WAY100635 (0,1 mg / kg i.p.) was started. Finally, behavioral responses of anxiety-like (Elevated plus maze – EPM test) and depression-like (modified forced swimming test - mFST) were evaluated and the analysis of the diabetic condition per se, such as glycemia, weight gain and plasma insulin levels was also performed. The procedures were approved by Ethics Committee for the Use of Animals of the Biological Sciences Sector of the Federal University of Paraná (#1106).

Results: Our findings show that CBD treatment, at the highest dose, was able to increase the weight gain and the plasma insulin levels, while the glycemia was reduced. These compound reduced the more expressive anxiogenic-like and depressive-like behavior of diabetic animals, which were associated with the reestablishment to the basal levels of the altered 5-HT, NA and/or DA levels in PFC and HIP from DBT animals. Moreover, the treatment with the 5HT1A receptor antagonist was able to block the anxiolytic-like and antidepressant-like behaviour of the CBD in diabetic animals.

Conclusion: Thus, repeated CBD treatment seems to have therapeutic and neuroprotective profile and could be a good candidate to treat anxiety/depression associated with diabetes.

Oral

SUMOylation as a potential target for Alzheimer's disease

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Background: SUMOylation acts as a biochemical switch in many pathways through regulating the function of a vast array of proteins, and is thus crucial in all eukaryotic cells. It has emerged recently that SUMOylation is involved in multiple neuronal signalling cascades and is implicated in many neurodegenerative diseases, including Alzheimer's disease (AD).

Objectives: We are currently investigating the global SUMOylation levels and the effects of manipulating SUMOylation and deSUMOylation pathways in cultured neurons, astrocytes and animal models of AD. In particular, we are focusing on the role of potential SUMO targets relevant to mitochondrial dysfunction, such as Drp1, a GTPase that regulates mitochondrial fission, and interacting proteins, such as Mff.

Methods: We examined changes in protein SUMOylation, and proteins involved in mitochondrial dynamics, in an in vitro model of AD induced by application of amyloid-β 1-42 (Aβ1-42) to cultured neurons.

Results: We observed Aβ1-42-induced decreases in global SUMOylation and in levels of the SUMO pathway enzymes SENP3, PIAS and SAE2. Aβ exposure also decreased levels of the mitochondrial fission proteins Drp1 and Mff and increased activation of caspase-3. To examine whether loss of SENP3 is cytoprotective we knocked down SENP3, which partially prevented the Aβ1-42-induced increase in caspase-3 activation.

Conclusion: Together, these data support the hypothesis that altered SUMOylation may play a role in the mechanisms underlying AD.

Poster

Prolonged Treatment with a Phosphodiesterase 4 Inhibitor did not Induce Anxiety-like Behavior or Negative Affective State in Rats

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Background: Phosphodiesterase-4 (PDE4) is an enzyme that catalyzes the hydrolysis of cyclic AMP (cAMP) and is involved in various central nervous system conditions, including depression, learning and memory, and anxiety. This important role in anxiety is due to its strong expression in brain regions such as the prefrontal cortex, hippocampus and amygdala [1]. The elevated plus maze (EPM) is a widely used behavioral assay for rodents to assess the anxiety-like behavior, however different parameters such as ultrasonic vocalizations (USV) could provide a detailed behavioral analysis, since this kind of communication can indicate different affective states, whether representing rewarding situations and positive affect (50 kHz USV) or negative/aversive states of fear

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and/or anxiety (22 kHz USV) [2]. Roflumilast (a phosphodiesterase 4 inhibitor) has shown positive effects in animal models of memory impairment [3]; however, other PDE inhibitors showed increase in anxiety-like behaviors [1,4].

Objectives: Therefore, the aim of this study was to investigate the effects of repeated roflumilast administration in the EPM and USV in the Open-field arena in Wistar rats. Nayve

Methods: Nayve animals were treated with roflumilast (0.01 mg/kg; 0.03 mg/kg or 0.1 mg/kg i.p.) or vehicle during 13 consecutives days and submitted to behavioral testing on the following order: first, they were exposed to USV and Open field test, and immediately after they were tested in the EPM (CEUA #1219).

Results: The results showed that roflumilast did not induce any changes neither in the EPM parameters (% of entries and time spent in the open arms, and also in the number of close arms entries) nor in the USV (frequency of both 22 kHz and 50 kHz). There was no change in locomotor activity in the Open-field arena (number of crossed lines).

Conclusion: Thus, these preliminary results suggest that roflumilast, at these treatment schedules, did not induce anxiety-like behavior or negative affective state, which is interesting for its clinical use.

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Poster

Effects of inhibition of the endocannabinoid 2-AG hydrolysis in the dorsolateral periaqueductal gray matter of rats in the contextual fear-conditioning test

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Background: Introduction: Anxiety disorders are characterized by exacerbated defensive responses, they significantly impair quality of life and better pharmacological treatment options are required [1]. The endocannabinoid system is a promising target for the development of new drugs for such disorders [2][3]. This neurotransmission system consists of the endocannabinoids: 2-arachidonoylglycerol (2-AG) and Anandamide (AEA). The 2-AG exerts its effects through activation of cannabinoid type 1 (CB1) and type 2 (CB2) receptors and modulates responses to aversive stimuli in various regions of the brain, including dorsolateral periaqueductal gray (dlPAG) [4][5]. However, its role on the expression of contextual fear responses mediated by the dlPAG is still unclear.

Objectives: Thus, the aim of this work was verify whether inhibition of 2-AG hydrolysis in the dlPAG attenuate behavioural response of rats submitted to a contextual-fear paradigm.

Methods: Methods: Male Wistar rats (n = 6-10 / group) received cannula implants in the dlPAG. Seven days later, they were submitted to Contextual Fear Conditioning (CFC) Test chamber for habituation period, followed by a conditioning section (foot electric shocks, 6 cycles, 1.5 mA randomized, duration of 3s) for 10min. After 24h, they received intra-dlPAG injection of vehicle or JZL184 (3, 10 and 30 pmol/ 0.2 µL) or URB602 (30, 100, 300 and 1000 pmol/ 0,2 µL). Ten minutes later, each animal was re-exposed to the test chamber and the time spent in freezing was recorded for 10 min. [CEUA: 66/2010]. To investigate the cannabinoid receptor involved in response mediated by JZL184, the animals were pre-treated with the CB1 and CB2 receptor antagonists, AM251 and AM630, respectively.

Results: Results: The administration of JZL184 (10 pmol) significantly reduced the animal's freezing time as compared to animals from vehicle [$F(3,30)=3.31$ $p = 0.03$, ANOVA followed by Bonferroni]. Any doses of URB602 modified animal´s behavior ($F(4,37) =.0.77$ n.s). The antagonists prevented the effects induced by JZL 184.

Conclusion: Conclusion: JZL 184 has a higher selectivity than URB 602 to inhibit 2AG hydrolysis, suggesting its effects could be due facilitation of 2AG signaling during expression of contextual fear. These results reinforce the involvement of 2AG in the inhibition of aversive states modulated by dlPAG.

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Poster

Sex differences in the behavioral response of serotonergic inhibition of the medial pre-frontal cortex in rats submitted to the forced swimming test

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Background: The forced swimming test (FST) is a behavioral test developed to assess the effects of antidepressants (AD) in rodents [1]. Male rats

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administered with AD such as SSRIs presented low scores of immobility in the FST, which is considered an antidepressant-like effect. Furthermore, the injection of the GABA-a agonist muscimol in the infralimbic cortex (IL), a sub region of the prefrontal cortex of rats, also promoted an antidepressant-like effect by inhibiting IL activity [2].

Objectives: Here, it is hypothesized that the increase in serotonergic transmission, which also may inhibit IL activity, would promote an antidepressant-like effect in rats. Since sex differences in the antidepressant responses has been observed in rodents and humans

Methods: Male and Female Wistar rats, 90 days old, were submitted to stereotaxic surgery for implantation of guide cannulae towards IL. After 7 days of recovery, rats were submitted to the pre-test session (15 minutes) of the FST followed by a test (5 minutes) 24 hours later. Intra-cortical infusion of 1 ul/1 min of either vehicle, Muscimol (200pmoles, n=8), 8-OHDPAT (10nmols, 5ht-1a agonist, n=8), WAY100635 (30nmols, 5ht-1a antagonist, n=8) or WAY100635+8-OHDPAT (30nmols+10nmols, n=8) occurred 10 minutes prior to the test. Immobility time was scored in the videotaped test with the aid of the Ethowatcher [3].

Results: Infusion of Muscimol reduced the immobility time in both males and females (males: 49.43±8.36; females: 47.60±9.26). The infusion of 8-OHDPAT reduced immobility time in males (46.97±15.31), but not females (80.56±13.52). Effects of 8-OHDPAT in males were counteracted by the previous infusion with WAY100635 (129.54±27.44).

Conclusion: Although the GABAergic inhibition of the IL was able to reduce immobility time in rats of both sexes, the same was not true for the serotonergic inhibition. Therefore, we suggest that females may be more resistant to the serotonergic inhibition of the IL, pointing to a sexual dimorphism of serotoninergic system in this region.

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Poster

Food deprivation and search for palatable food in fruit flies: interactions between sex and duration of fasting

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Background: The use of vertebrates in biomedical research has been criticised in the field of animal ethics and welfare. So, the scientific community has been seeking to implement "3Rs" (reduction, refinement, replacement). The substitution of vertebrates with invertebrates is a form of reduction or partial replacement of vertebrates in biomedical sciences [1]. Drosophila melanogaster is invertebrate used in different areas of research. As other laboratory animals, D. melanogaster exhibited behavioral changes such as low consumption of palatable food when exposed to a stressor [2].

Objectives: In this study, the objective was to verify the influence of two different periods of fasting on the search of palatable food in D. melanogaster.

Methods: Adults (7 to 10 days) male (m) and female (f) flies undergone two or eight hours (h) of fasting (fs) before behavioral testing (n=5 to 6/group). Control (c) groups (n=5 to 6/group) had access to food (corn medium) ad libitum. Flies (m or f) were removed from the "home glass" on the day of the experiment and placed in plastic tubes containing corn medium (c groups) or a water-soaked filter paper (fs groups). After 2 or 8 h, all flies were anaesthetised on ice (± -4°C) and placed individually in a lane of an apparatus for the behavioural testing, which was a plate with ten lanes. On the right extreme of a lane there was capillary (d: 0.4 mm) filled with 5% sucrose solution. Tests were videotaped for 60 min for further analysis. Latency, frequency and duration of locomotion and immobility in any region of the lane or on the capillary were scored with the aid of the software Ethowatcher BetaOS48.

Results: Behavioral analysis indicated that, in control conditions, females explored the lane or the capillary longer than males (lane: fc2h 723.6±165.1s; fc8h 782.8 ±236.5s; mc2h 496.5±224.2s; mc8h 544.1±151.2; capillary: fc2h 119±35.98s; fc8h 180.2±70.11s; mc2h 53.48±28.4s; mc8h 100.2±29.36s). Conversely, immobility of males was longer than females (lane:fc2h 2656±194.8s; fc8h 2480.06 ± 303.8s; mc2h 2894±256.8s; mc8h 2858.66±169.3s; capillary: fc2h 41.6±22.4s; fc8h 31.7±10.75s; mc2h 113.3±110.6s; mc8h 9.17±5.2s). In fasting conditions, females explored the lane or the capillary longer than males (lane: ffs2h 762±268.1s; ffs8h 300.85±121.7s; mfs2h 291.4±113.2s; mfs8h 304.15±88s; capillary: ffs2h 165.4±69.28s; ffs8h 62.6±30.49s; mfs2h 74.7±20.3s; mfs8h 58.6±18.6s). Immobility times of males were longer than females (lane: ffs2h 2571±339s; ffs8h 3064±135.8s; mfs2h 3083±108.3s; mfs8h 3091±104.6; capillary: ffs2h 23.20±7.6s; ffs8h 23.7±14.6 s; mfs2h 67.4±43.2s; mfs8h 12.84±6.26s).

Conclusion: In summary, females were more mobile than males in most experimental conditions, except

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after eight hours of fasting. Fasting for two hours had little effect on the exploration of the lane by females or males. Fasting for eight hours decreased exploration of any part of the lane, including the capillary, in females and males.

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Poster

Aerobic exercise attenuates hyperalgesia signs induced by fibromyalgia model

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Background: Fibromyalgia (FM) is a chronic condition causing pain and sleep disturbance, fatigue, depression, anxiety, mood disorders, irritable bowel and other symptoms, which negatively impact the quality of life [1]. Although it's an etiology is still not well understood, FM is considered a neurobiological disease caused by abnormal processing of pain [2,3]. The complexity of the syndrome is also reflected by the fact that pharmacological, non-pharmacological and cognitive behavioral treatments do not seem to be efficacious [3]. Currently, there is a constant search for new therapeutic options that minimize the impact of FM on patients' quality of life [4]. Moreover, there are recent evidence that physical exercises inhibit pain and fatigue symptoms in FM patients, although there is no consensus about the type, frequency, duration, and intensity of beneficial physical activity for this population [5].

Objectives: Herein, we evaluated the effects of moderate and high-intensity aerobic exercise in hyperalgesia induced by FM model.

Methods: Female Swiss mice were used for FM induced by reserpine subcutaneous administration in a volume of 1 ml/kg and at a concentration of 0.25 mg/kg, once daily for 3 consecutive days and the exercise protocols lasted two weeks. All experimental procedures were approved by the UFSC Committee on the Ethical Use of Animals and were carried out in accordance with Brazilian regulations on animal welfare (CEUA/UFSC protocol number 2572210218).

Results: Our data showed that both moderate and high-intensity aerobic exercise protocols consistently reduced spontaneous pain during FM model. Furthermore, moderate intensity exercise significantly reduced mechanical allodynia response. Moreover, exercise protocols demonstrated to be more effective than positive control – a commercially pattern drug – in the analgesia to the cold stimulus.

Conclusion: In conclusion, our data suggest that regular physical exercise of moderate to high intensity may represent an important non-pharmacological intervention for treatment of hyperalgesia induced by FM.

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Poster

Oxytocin receptor modulates anxiogenic like behavior in psychological stress

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Background: Oxytocin (Oxt) is a nonapeptide massively produced by hypothalamic structures. Oxt has a wide neural network with receptors (OxtR) that can be activated by Oxt either locally produced or secreted from the hypothalamus. In stressful situations, occurs Oxt release and activation OxtR, dependent on the stress type whose functions are yet not completely understood. There are reports showing pro-social, anti-aggressiveness and anxiolytic effects of Oxt. Psychological stress induces Oxt increases both centrally and in the periphery. Acute restraint stress (ARS) is a psychological stress model that produces autonomic, neuroendocrine and behaviors changes, as well as late anxiety behavior. Objectives: The present study aimed to evaluate Oxt release and behavioral alterations induced by ARS, and using pharmacological manipulation, to study how Oxt modulates these responses.

Methods: This project was approved by Ethical Committee (CEUA 079/2017). Sprague-Dawley rats, weighing 250-300 g were subjected to ARS for 180 min and subjected to behavioral tests 24 hours later: open field (OF), and elevated-plus maze (EPM). Animals were divided into naïve and treated groups:

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Naïve (Non-treated or stressed rats), vehicle, OxtR antagonist L-368,899 (0,3, 1 and 3 micrograms/kg, i.p.) or diazepam (1 mg/kg, i.p. positive control for behavioral analyses). Oxt quantification was made in an independent group; the animals were immediately sacrificed after ARS and blood collected to measurement of OXT by radioimmune assay.

Results: None of the treatments altered spontaneous locomotion assayed in the OF, however, stressed animals treated with vehicle or OxtR antagonist in all doses presented anxiety-like behavior characterized by a reduced time spent on central quadrants in OF. To confirm this result, we performed EPM. Stressed animals presented a reduction in the percentage of open-arms entries (%OAE) and time (%OAT), and animals treated with OxtR antagonist presented increased anxiety-like behavior in %OAE, L-368,899 (1 micrograms/kg) vs. Naïve ($P<0.05$); vs. Vehicle (stressed; $P<0.05$). The same decrease in %OAT was observed after L-368,899 (0,3 micrograms/kg) vs. Naïve ($P<0.05$); vs. Vehicle (stressed; $P<0.05$); and in L-368,899 (1 micrograms/kg) vs. Naïve ($P<0.05$); vs. Vehicle (stressed; $P<0.05$), without alteration in the locomotion in EPM, as well as entries and time spent in closed-arms. ARS evoked increase in the concentration of plasma Oxt, and a tendency to a higher increase in plasma Oxt was observed in the group vehicle when compared to Naïve. Treatment with L-368,899 reduced ARS-evoked increase in Oxt concentration in a dose-dependent manner.

Conclusion: Our results showed that plasma Oxt increase in response to ARS, a psychological stressful model, is important to attenuate the late anxiety-like behavior produced by ARS. Furthermore, the treatment with Oxt antagonist produces an additive effect to stress, and reduces plasma Oxt concentration, which may be a correlate of central decreased Oxt..

Poster

Effects of the cannabidiol on aversive memory expression and reconsolidation in female rats

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Background: Associative aversive learning is essential for individuals to cope with dangerous and stressful stimuli present in an ever-changing environment. Upon recall, aversive memories can be expressed and destabilized-reconsolidated. The cannabidiol (CBD), a non-psychotomimetic compound from Cannabis, has been shown to attenuate the contextual fear memory expression and reconsolidation in male rat studies. It is unknown whether these CBD effects are similarly observed in females, which tend to express less conditioned freezing against aversive contextual cues than males.

Objectives: The present study sought to investigate the CBD effects on expression and reconsolidation of a contextual aversive memory in female rats. Considering that estrous cycle- dependent effects on freezing time have been reported in certain aversive learning pa

Methods: Methods. Adult females Wistar rats were initially contextually-fear conditioned. On the next day, they were randomly allocated to four groups based on the systemic treatment (VEH or 1.0, 3.0 or 10 mg/kg of CBD) given before the exposure to the paired context for 5 min (experiment 1). In experiment 2, contextually-fear conditioned females were allocated to six groups based on the estrous cycle phase (proestrus, estrous or diestrous) and the treatment (VEH or CBD 10 mg/kg) given prior to the paired context exposure for 5 min. In experiments 3 and 4, animals were exposed to the paired context for 2 min to destabilize the memory and then treated systemically or bilaterally into the dorsal hippocampus with VEH or CBD. In experiment 5, animals were treated with VEH or CBD 6 h after the exposure to the paired context for 2 min to investigate whether the CBD effects on reconsolidation are still present. In experiment 6, animals were treated with VEH or CBD in the absence of a memory destabilization session, which is the prior step to reconsolidation.

Results: Females treated with CBD (10 mg/kg) expressed less freezing time than respective controls during exposure to the paired context (experiment 1). This anti-aversive effect of the CBD remained unchanged across the estrous cycle (experiment 2). Not only systemic but also intra-dorsal hippocampus administration of CBD impaired the memory reconsolidation process (experiments 3 and 4) once drug-treated animals presented lower freezing time than respective VEH-treated animals. The memory reconsolidation disruption induce by CBD was no longer observed when it was given 6 h after the destabilization session (experiment 5) or when it was omitted (experiment 6).

Conclusion: The present findings provide evidence that CBD attenuates the contextual aversive memory expression and reconsolidation in females regardless of their estrous cycle phase. This pattern of results is similar to that previously reported in male animal studies.

Oral

The Role Of The Nociceptin/Orphanin FQ Receptor System In The Modulation Of Mood Disorders

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Background: Nociceptin/orphanin FQ (N/OFQ) and its receptor (NOP) were identified with the reverse pharmacology approach as a peptidergic system structurally related to opioids. The peptide N/OFQ and its receptor are widely expressed in the nervous system as well as in peripheral organs and the immune system. A large variety of central biological functions have been described to be modulated by the N/OFQ-NOP receptor system, such as emotional states, pain transmission, food intake, locomotor activity, learning and memory, and drug abuse.

Objectives: This study summarizes the most relevant findings which support the NOP antagonists-induced antidepressant actions.

Methods: A wide variety of preclinical models, NOP antagonists, and NOP knockout animals were used for assessing the effects of the blockade of NOP receptor signalling in mood disorders. Additionally, clinical studies were also developed for investigating the relationship between N/OFQ system in major depression.

Results: Preclinical evidence suggests that blockade of NOP receptors evokes antidepressant-like actions. These have been shown using distinct compounds (peptide and non peptide antagonists), across different species (rat and mouse) and assays (behavioral despair, chronic mild stress, LPS-induced depressive-related behaviors and learned helplessness model) suggesting a robust and consistent antidepressant-like effect. Moreover, rats and mice knockout for the NOP receptor display an antidepressant-like phenotype in behavioral despair tests, LPS-induced depressive-like effects and learned helplessness model. Electrophysiological, immunohistochemical and neurochemical studies point to an important role played by monoaminergic systems and neurotrophic factors (mainly FGF-2) in mediating the antidepressant-like properties of NOP antagonists. The relationship between the N/OFQ-NOP receptor system in the modulation of stress responses is under investigation. Recent findings from our research group suggest that NOP antagonists prevent the development of stress-induced depressive-like behaviors. Clinical studies showed that plasma N/OFQ levels were significantly elevated in post-partum and bipolar depression patients. Recently, a proof-of-concept study showed that once daily oral dosing of LY2940094 at 40 mg for 8 weeks vs placebo provided some evidence for an antidepressant effect assessed by the GRID-Hamilton Depression Rating Scale.

Conclusion: Literature data support the notion that NOP antagonists are promising candidates for the development of innovative antidepressants.

Poster

Accumbal endocannabinoid signaling mediates cocaine craving following prolonged abstinence

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Background: Cue-induced cocaine craving is a cardinal characteristic of cocaine use disorder. Cocaine craving progressively intensifies during abstinence leading to perpetual relapse vulnerability. Endocannabinoid signaling in the nucleus accumbens (NAc) mediates synaptic depression associated with rewarding properties and contributes towards cocaine-induced behavioral attributes; however, the role of accumbal endocannabinoid signaling in incubation remains to be investigated.

Objectives: This study was designed to test the hypothesis that the endocannabinoid system would be involved in regulation of cocaine craving following prolonged abstinence

Methods: Expression of enzymes that regulate synthesis (diacylglycerol lipase-DAGL) and breakdown (monoacylglycerol lipase-MAGL) of endocannabinoid 2-Arachidonoylglycerol (2-AG) were examined on withdrawal day (WD) 1 and 30 following extended-access cocaine self-administration . To determine a causal role of 2-AG in cue-induced cocaine seeking, we performed pharmacological inhibition of DAGL and MAGL in the nucleus accubens. Finally we investigated if the increase in 2-AG signaling, promoted by inhibition of MAGL, would modulate the phosphorylation of eukaryotic initiation factor 2 (eIF2α).

Results: DAGL was increased while MAGL was decreased in the NAc on AD30 but not on AD1 following extended-access cocaine SA. Intra-accumbal microinjection of DAGL inhibitor DO-34 attenuated, while the MAGL inhibitor URB-602 increased, cocaine seeking on AD30, demonstrating that 2-AG-mediated endocannabinoid signaling regulates cocaine seeking during prolonged withdrawal. Dephosphorylation of eIF2α was previously shown to mediate cocaine seeking during prolonged abstinence, and we found that inhibiting MAGL resulted in dephosphorylation of eIF2α in the NAc, suggesting that cocaine seeking during prolonged abstinence is mediated through a mechanism involving altered phosphorylation of eIF2α by 2-AG.

Conclusion: Together, these results demonstrate bidirectional regulation of cue-induced cocaine craving by 2-AG signaling in the NAc during prolonged abstinence.

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Poster

Role of μ-opioid and CB1 receptors of the dorsal periaqueductal gray matter in the modulation of aversive and antinociceptive responses induced by fear

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Background: A wealth of evidence indicates that the activation of CB1 and μ-opioid receptors (MOR) in the dorsal periaqueductal gray matter (dPAG) inhibits more intense fear-like responses. Given that the aversive dPAG stimulation also induces an antinociceptive effect.

Objectives: we propose to investigate the role of cannabinoid and opioid system in dPAG on antiaversive and antinociceptive effects mediated by the dPAG chemical stimulation.

Methods: For that, the basal thermal threshold was evaluated using the tail-flick test. In the next day, the animals received intra-dPAG injection of CB1 receptor-selective agonist ACEA (0.5 pmol/0,2 μL), CB1 receptor antagonist AM251 (100 pmol/0,2 μL), MOR agonist DAMGO (0.5 pmol/0,2 μL), MOR antagonist CTOP (0,1 nmol/0,2 μL) or its vehicle (0,2 μL) followed by the intra-dPAG injection of N-methyl-D-aspartate (NMDA, 1 nmol/0,2 μL) to evaluate aversive responses - freezing and crossing behaviors - in free-moving animals. Immediately after, the thermal threshold was evaluated again. All procedures were approved by the Research Ethics Committee for the Use of Animals of the Biological Sciences Sector of the Federal University of Paraná (#1188).

Results: The CB1 receptor agonist and MOR agonist, but not its respective antagonists, prevented the NMDA-induced aversive responses. While the CB1 agonist did not alter the antinociceptive effect induced by aversive chemical stimulation in the dPAG with NMDA, the MOR agonist induced a more marked antinociceptive effect when compared to vehicle-treated animals chemically stimulated with NMDA.

Conclusion: Our findings indicate a beneficial effect of the activation of CB1 receptor and MOR into dPAG on aversive behavioral consequences of chemical stimulation of dPAG, highlighting that the activation of MOR in the dPAG enhances the fear-induced antinociception.

Poster

Fluoxetine enhances the anxiety-like behavior induced by the elevated T-maze in mice

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Background: The elevated T-maze (ETM) is a rodent model for studying the role of serotonin (5-HT) in the regulation of defensive behaviors associated with anxiety and panic [1]. The open field test (OFT) allows evaluating exploratory behavior, spontaneous locomotion and emotionality in rodents. It involves forced confrontation with a situation in which rodents spontaneously prefer the periphery of the apparatus to the central zone, a behavior called thigmotaxis. An increase of time spent in the central zone and consequent reduction in periphery time are indicatives of anxiolysis [2]. Fluoxetine (FLU) is an antidepressant also used for treating panic and generalized anxiety disorders, which selectively inhibits neuronal serotonin transporter (SERT) [3]. The stimulation of 5-HT2C receptors in the basolateral amygdala increases anxiety and is implicated in the anxiogenesis caused by short-term administration of antidepressant drugs [1].

Objectives: In this context, the aim of this study was to evaluate the effect of association between ETM exposure and FLU treatment on behavioral responses of mice in the OFT.

Methods: Adult male CF1 mice were treated with FLU (30 mg/kg, p.o.) or saline plus polysorbate 80% (VEH) 90 min before being evaluated in the OFT. VEH and FLU treated mice were or not exposed to ETM for 30 min [4], therefore comprising four groups: VHC - mice not exposed to ETM and treated with VEH; FLU- mice not exposed to ETM and treated with FLU; ETM-VEH- mice exposed to ETM and treated with vehicle; ETM-FLU- mice exposed to ETM and treated with FLU.

Results: ANOVA two way revealed that the exposure to ETM increased the immobility time ($F_{exposure}(1,39) = 20.465$, $P<0.001$; $F_{treatment}(1,39) = 0.007$, $P=0.990$; $F_{interação}(1,39) = 2.165$, $P=0.150$) in the OFT. The ETM exposure and treatment reduced the travelled distance ($F_{exposure}(1,39) = 37.045$, $P<0.001$; $F_{treatment}(1,39) = 20.505$, $P<0.001$; $F_{interação}(1,39) = 7.391$, $P<0.01$), and FLU reduced the travelled distance in the ETM group only ($P<0.001$). ETM exposure and treatment increased the periphery zone time ($F_{exposure}(1,39) = 18.664$, $P<0.001$; $F_{treatment}(1,39) = 8.69$, $P<0.01$; $F_{interação}(1,39) = 3.796$, $P=0.059$) FLU increased the periphery time in the ETM group ($P< 0.01$). In turn, the central zone time decreased in mice previously exposed to ETM ($F_{exposure}(1,39) = 18.477$, $P<0.001$; $F_{treatment}(1,39) = 13.133$, $P<0.001$; $F_{interação}(1,39) = 2.988$, $P=0.092$). FLU reduced the central zone time in the ETM group only ($P< 0.01$).

Conclusion: The exposure of mice to elevated T-maze provokes an anxiety-like behavior in the open field test,

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which is enhanced by the acute administration of fluoxetine. This is in line with other studies [5] demonstrating that the behavioral effects of acute fluoxetine administration resemble those produced by uncontrollable stress. Ethical Approval: CEUA-UFRGS 33959 Acknowledgements: CNPq fellowships and CAPES-PROEX 0477/2017.

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Oral

Stress during sensitive periods of development and risk for schizophrenia

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Background: External stressors are known to contribute to the pathogenesis of psychiatric disorders, including schizophrenia. However, the impact of stress can vary depending on the timing and the length of exposure. Adolescence, as a developmental period of heightened plasticity, is proposed to be particularly sensitive to environmental insults, as opposed to adulthood.

Objectives: In this talk, I will present data showing the impact of adolescent and adult stress on the ventral tegmental area (VTA) dopamine (DA) system activity.

Methods: We carried out electrophysiology recordings and behavioral tests.

Results: Adolescent stress induced both short- and long-term schizophrenia-like changes in the ventral tegmental area (VTA) dopamine (DA) system, as indicated by the increased VTA DA neuron population activity and the augmented locomotor response to amphetamine. In contrast, adult stress only produced short-term changes consistent with models of depression, as indicated by the decreased VTA DA neuron population activity, which failed to persist after 5-6 weeks. However, when the stressors were applied concurrently with sodium valproate, a putative "critical period" re-opener that increases neural plasticity through inhibition of histone deacetylase, adult stress increased VTA DA neuron population activity similar to that occurring with adolescent stress.

Conclusion: These findings suggest that 1) timing of stress is a critical determinant of the circuit pathology in adult, 2) adolescent stress may be a precipitating factor for the transition to psychosis, and 3) re-opening the critical period of plasticity in the adult recreated an adolescent phenotype of restored vulnerability to a stress-induced pathology of schizophrenia. These data will be discussed taking into account the closure of the critical period of plasticity by the development of the perineuronal nets, a glycosaminoglycan matrix sheath that surrounds mainly the parvalbumin GABAergic interneurons and stabilizes glutamatergic inputs to limit the plastic phase in the adult brain.

Poster

Social behavior and endocannabinoid-mediated plasticity in the nucleus accumbens of adult mice exposed to win55,212-2 during juvenile period

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Background: Drug exposure during critical periods of development is known to have lasting effects, increasing the risk for developing mental health disorders. Cognitive alterations resulting from the use of Cannabis are complex and may be present even after cessation of consumption. Adolescence is characterized by endocannabinoid (eCB)-dependent refinement of neural circuits underlying emotion, learning and motivation. Chronic exposure to cannabinoid agonists during adolescence alters social behavior and nucleus accumbens (NAc) molecular mechanisms in adult rodents. However, sex differences on social behavior as well as NAc synaptic plasticity after chronic cannabinoid exposure in adolescence remain poorly explored.

Objectives: Thus, we aimed to investigate long-term consequences of a chronic exposure to a cannabinoid agonist during juvenile period in the social behavior and eCB-mediated synaptic plasticity in NAc in mice of both sexes.

Methods: Male and female Swiss mice (Ethical approval: APAFIS#$3279-2015121715284829 v6) were exposed to WIN 55,212-2 (WIN) 2 mg/kg i.p. daily from post-natal day (PND) 28 to 37. Control mice received vehicle (DMSO 5%, cremophor 5% and saline 90%). Social approach and eCB-mediated long-term depression (LTD) in the NAc were evaluated at adulthood (PND>70) in both male and female mice.

Results: WIN-exposed male mice showed preference for the social cage in social approach similarly to control group (Control: n=9, p=0.001; WIN: n=8, p=0.049, Student-t test). Low-frequency stimulation of excitatory synapses onto NAc medium spiny neurons induced a robust eCB-LTD in both control and WIN-exposed males (Control: n=5, p=0.028; WIN: n=9, p<0.001; paired t-test). Similarly, no alterations were

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observed in female mice exposed to WIN (Control: n=2; p=0.178; WIN: n=3; p=0.129, paired t-test).

Conclusion: Together, these results show that sociability and eCB-mediated synaptic plasticity in the NAc are not altered in both male and female adult mice daily exposed to WIN during the juvenile period. **Financial support**: CAPES (88881.190118/2018-01 to PFRG), CNPq (200843/2015-1 to MB), Institut National de la Santé et de la Recherche Médicale (INSERM), Fondation pour la Recherche Médicale (Équipe FRM 2015 to OM) and the NIH (R01DA043982 to OM). patriciarolo@gmail.com.

Oral

Cannabinoid and Anxiety Treatment

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Background: The anxiolytic properties of the Cannabis sativa plant have been known for centuries. However, it was only after the isolation of its main active compound, delta-9-tetrahydrocannabinol (THC) and the discovery of the endocannabinoid (eCB) system that the mechanisms of these properties have been systematically investigated. Several pieces of evidence now indicate that the eCB system plays a crucial role in fear memory processes.

Objectives: Facilitation of eCB-mediated signaling, for example, enhances conditioned fear memory. Initial clinical studies indicate that this approach could be helpful in the treatment of post-traumatic stress disorder (PTSD) [1].

Methods: Cannabidiol (CBD) is another major non-psychotomimetic compound present in the plant. Single-dose studies using this compound showed that it induces anxiolytic effects in humans and in animal models associated with several anxiety and stress disorders, including panic and PTSD. These effects depend, mostly, on facilitation of post-synaptic serotonin-1A (5HT1A)-mediated neurotransmission in brain sites related to defensive responses, such as the medial prefrontal cortex, bed nucleus of the stria terminalis, and dorsolateral periaqueductal grey. Although the mechanisms responsible for this facilitation are still unclear, they could involve an increase in serotonin levels, interactions with allosteric binding sites in the receptor, or interference with intracellular pathways.

Results: The long-term anxiolytic effects of CBD in chronically stressed mice, however, are associated with neuroplastic effects such as an attenuation of the stress-induced decrease in hippocampal neurogenesis and synaptic remodeling. These effects depend on CB1 and CB2 cannabinoid receptors rather than 5HT1A, and probably involve an indirect increase in the levels of the endocannabinoid anandamide due to inhibition of its metabolism[2].

Conclusion: Taken together, these results indicate that cannabidiol and other drugs targeting the endocannabinoid system could be helpful in the treatment of anxiety disorders. Acknowledgements: This work was supported by grants from FAPESP (2017/24304-0) and the National Institute of Science and Translational Medicine, CNPq (465458/2014-9)

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Poster

Modulation Of The Nop Receptor Signaling Affects Stress Coping Responses In Mice: Implications For Resilience To Stress

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Background: The peptide nociceptin/orphanin FQ (N/OFQ) and its receptor (NOP) are largely implicated in the modulation of emotional states [1]. Clinical and preclinical findings support antidepressant effects due to the blockade of NOP receptor signaling [2]. However, it is unclear the involvement of the endogenous N/OFQ – NOP receptor system in mediating stress coping strategies.

Objectives: The present study investigated the effects of activation or blockade of the NOP receptor signaling before exposure to acute stress.

Methods: Male CD-1 and female Swiss mice and male NOP receptor knockout mice (NOP (-/-)) were used in this study. Mice were treated before stress exposition with the following drugs: nortriptyline, NOP agonists (Ro 65-6570 and MCOPPB) and NOP antagonist (SB-612111). Inescapable electric footshock (2 sessions; 180 cycles, 0.5 mA, 1-10 s shock duration, 1-20 s interval) and forced swim (2 sessions: 15-min training session + 5-min test session) were used as acute stressors. Mouse behavior was evaluated by assessing the percentage of helpless phenotype (<20 escapes/30 trials) in the inescapable footshocks and time spent immobile in the forced swim. All the experiments were approved by ethics committees from UFRN (N° 059/2015; Nº 010.015/2017) and UNIFE- IT (Nº 302/2017).

Results: The activation of the NOP receptor signaling with the agonists Ro 65-6570 (0.01-1 mg/kg, ip) and MCOPPB (0.1-10 mg/kg, ip), before inescapable footshocks and swim stress, increased the percentage of mice developing helpless behavior and facilitated

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immobile posture, respectively. In contrast, the blockade of NOP receptor with the antagonist SB-612111 (1-10 mg/kg, ip) reduced the acquisition of depressive-like phenotypes, and similar resistance to develop helpless behaviors was observed in mice lacking the NOP receptor. Under the same stressful conditions, administration of the antidepressant nortriptyline (20 mg/kg, ip) did not change acquisition of helpless behavior and immobile posture.

Conclusion: These findings support the view that NOP agonists during acute stressful events facilitate depressive-related behaviors, whereas NOP antagonists have a protective outcome. The present study showed for the first time that the N/OFQ - NOP receptor system is a relevant player in controlling resilience to stress and development of depressive states

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Poster

Effects Of A TRPV1 Blocker In The Dorsolateral Hippocampus In The Contextual Fear Conditioning Model

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Background: The TRPV1 channel was recently related to anxiety and specifically with aversive memory in several models and anatomic structures [1,2]. On the other hand, studies point to limitations of TRPV1 as pharmacological target due to its different expression along the development. The peak of TRPV1 expression was found at week eight in C57BL6/J mice [3].

Objectives: The aim of this study was the evaluation of SB336791, a TRPV1 blocker, in the contextual fear conditioning model in the dorsolateral hippocampus (dlHPC) comparing the activity of this drug in different stages of development.

Methods: C57BL6/J MALE mice from the animal facility of UFMG (CEUA: 78/2014), with 9 or 22 weeks, were subjected to stereotaxic surgery to bilateral cannulation of the dlHPC. Five to seven days later the behavioural experiment was performed. The first day the animals were exposed to the conditioning box and received a 1 or 2 sec shock. The second day the animals were separated in groups receiving vehicle or SB336791 (1, 3, or 10nmol) and re-exposed to the context. The variable quantified was the freezing time. Data were analysed by ANOVA followed by Newman-Keuls test and p-value was set at 0.05

Results: SB336791 3 nmol decreased the freezing time in 22-week-old animals after 1sec shock. Statistical analysis didn't reveal any difference in the 1sec protocol in 9-week-old animals. Preliminary results indicate that SB336791 1 nmol decreased freezing in the 2 sec protocol.

Conclusion: Differences in TRPV1 expression along the development didn't prevent the effects of SB336791. However, in 9-week-old animals increased levels of aversive stimulus seem to be required to TRPV1 be susceptible to pharmacological modulation.

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Poster

Conditioned Place Preference To Cocaine In Leptin Receptor Deficient Diabetic (Db/Db) Mice

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Background: The neurobiological mechanisms that regulate the response to addictive drugs are complex, and increasing evidence suggests an important role of appetite regulation in substance abuse [1,2]. Leptin, an important adipose hormone, whose circulating levels reflect the body's energy stores in adipose tissue, regulates energy balance and apetite via leptin receptors expressed in central nervous system [3]. Previous data indicate that leptin signaling is critically involved in cocaine-conditioned reward. The infusion of the leptin receptor antagonist during cocaine conditioning increased the cocaine-conditionated place preference [2] and the infusion of the leptin in nucleus accumbens core disrupts acute cocaine effects [4]. Complementing these findings in animals, the leptin serum levels is inversely correlated with the severity of crack use in humans [5]. Although data indicate that leptin signaling is inversely correlated with cocaine effects, the role of leptin signaling in regulating the intensity of the learned response to cocaine after this drug is no longer present remains unclear.

Objectives: Therefore, our objective was evaluate the reinforcing effects of cocaine and the persistence of memory of the conditioned reward response to cocaine in leptin receptor deficient diabetic (db/db) mice using a conditioned place preference (CPP) procedure.

Methods: The experimental protocol was approved by the Ethics Committee in Animal Experimentation of the Federal University of Minas Gerais (CEUA/UFMG 242/2013). The CPP test consisted of four phases, namely pre-conditioning (day 1), conditioning (days 2-7), testing (day 8), and extinction (days 9-14). For the procedure, male db/db mice and their wild-type (WT)

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littermates (16-20 weeks old) were given intraperitoneal injection of cocaine (15 mg/kg, days 3, 5 and 7) or vehicle (days 2, 4 and 6) immediately before they are placed in their respective drug-paired chamber of CPP apparatus. During the test and extinction phase, no drug was delivered and the time spent in each compartment was registered. The CPP index was calculated according to the time spent in the drug-paired side subtracted by the time spent in the vehicle-paired side [2].

Results: In the test session, both groups showed significant preference for the cocaine-paired chamber ($p<0.05$ different from pre-test session, Two-way ANOVA, followed by Bonferroni). However, during the extinction phase the db/db mice presented an impairment of the extinction response in the CPP test compared to WT mice ($p<0.05$, Two-way ANOVA).

Conclusion: Our data demonstrated that db/db mice displayed a more persistent memory of the cocaine-conditioned reward and suggest that the leptin signaling is also able to interfere in cocaine-CPP extinction phase.

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Poster

Pregabalin facilitates the acquisition of contextual aversive memory extinction and induces a long-lasting anxiolytic-like effect in diabetic animals

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Background: Clinical and preclinical studies show that diabetes mellitus impairs learning and memory processes. However, there is a lack of studies investigating aversive memory. In that way, our laboratory has shown that diabetic animals exposed to a contextual conditioned fear test present an impairment in extinguishing aversive memory and when tested in a neutral context they also present a fear response. Pregabalin is widely used for the treatment of diabetic neuropathic pain, but little is known about its impact on cognition and anxiety-like response associated with diabetes.

Objectives: Thus, the purpose of the study was to investigate the effect of pregabalin on the acquisition of contextual aversive memory extinction and on anxiety-like behavior in diabetic animals.

Methods: The procedures were approved by the Ethics Committee for the Use of Animals of the Biological Sciences Sector of the Federal University of Paraná (#1174). Male Wistar rats received one injection of streptozotocin (60 mg/kg; ip) to induce diabetes, the NGL animals received the citrate buffer. After three weeks, animals were subjected to a conditioned contextual fear protocol to evaluate the freezing time (index for fear memory). The protocol was composed by: contextual fear conditioning (3 shocks of 1mA with the 30s of the interval before and after each shock, 21st day, Session 1); extinction training (20min, 22nd day, Session 2); extinction test (3min, 23rd day, Session 3). The animals were injected with pregabalin (0; 30; 100 mg/kg, ip.), 1h before the extinction training (22th day). In addition, 7 days after the Session 3 the animals were submitted to elevated plus maze (EPM) test to evaluate behavioral parameters related to anxiety

Results: Our data showed that conditioned NGL animals presented a more pronounced anxiety-like behavior than non-conditioned NGL ($p <0.05$). However, DBT animals presented, besides an impairment in extinguishing the conditioned aversive memory, a more pronounced anxiety-like response when compared to conditioned NGL animals ($p <0.05$). Interesting, a single injection, immediately before the Session 2, of pregabalin was able to accelerate the acquisition of aversive memory extinction in DBT animals. Moreover, this single injection presented a long-lasting effect since the animals presented an anxiolytic-like effect when evaluated 7 days after session 3.

Conclusion: Taken together, our data indicate that pregabalin seems to have a therapeutic potential as an anxiolytic drug to treat anxiety and aversive memory related to diabetes.

Poster

Acute Treatment With Cannabidiol Did Not Prevent The Compulsive-Like Behavior In Mice After Consumption Of High-Refined Carbohydrate Diet

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Background: Obesity and their associated comorbidities, such as anxiety and depression are increasing over the past few decades [1]. The hallmark of obesity is the peripheral low-grade chronic

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inflammation, which could be associated to a neuroinflammatory process in the brain, facilitating the development of anxiety-related disorders [2,3]. In this context, cannabidiol (CBD), the main non-psychotropic phytocannabinoid present in the Cannabis Sativa plant, has emerged as a potential drug for the treatment of psychiatric [4]. Recently, some evidence has been proposed that CBD has an anti-inflammatory profile [5].

Objectives: Verify whether CBD could reverse the compulsive-like behavior observed after chronic consumption of high-refined carbohydrate (HC) diet in the Marble Burying Test.

Methods: Male Balb/c mice aged 6-7 weeks received a standard diet or HC diet for 12 weeks. After this, the animals received a i.p injection of vehicle or CBD (10mg/kg) and thirty minutes later were submitted to the Marble Burying Test (CEUA /UFMG: 65/2017).

Results: The animals from HC diet group displayed a compulsive-like behavior in the Marble Burying Test (Diet effect $F(1.24)= 5.59$, $p<0.05$; drug effect $F(1.24) = 0.49$, $p >0.05$; diet x drug effect $F(1.24)= 0.49$, $p >0.05$; Two-Way ANOVA). However, the pre-treatment with CBD did not prevent this effect.

Conclusion: Our results reinforced the compulsive-like effect induced by chronic consumption of high-refined carbohydrate diet. In our data we used a single dose of CBD, maybe a sub-chronic treatment would be necessary to prevent such effects. This hypothesis remains to be elucidated. ACKNOWLEDGMENTS: CNPQ,CAPES.

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Poster

The use of reliability measurements in the Forced Swim Test (FST) in rats: Probing the effects of experience on rater´s performance.

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Background: Estimates of intra-observer agreement using reliability indexes (such as Kappa) are strongly recommended to improve the reproducibility of FST and any other behavioral test based on direct human rating [1]. However, a recent systematic review [2] indicates very poor adherence to this recommendation in the FST literature. We examined different intra-observer reliability indexes (percent agreement [A%]; Cohen's- [CK], agreement by chance [AC%] and disagreement [%D]) to access the performance of experienced (EO) and novice (NO) observers in gathering FST data from rats.

Objectives: The present study aims to analyze and discuss the intraobserver agreement indexes of two experienced and one inexperienced observers in three videos of rats submitted to the Forced Swim Test experiment.

Methods: Two EO (1 and 2) and one NO raters, all trained using the Detke's [3] behavioral catalogue gathered frequency and duration of immobility (I), swimming (S), climbing (C) and diving (D) twice (with a 15-days interval between transcriptions), from the same three 5-min video recordings (V1, V2, V3) of FST tests in non-treated male rats. They used Ethowatcher® software for transcription, so to allow for frame-by-frame behavior identification, as well as calculation of A%, CK and FK indexes from the repeated transcriptions.

Results: Mean intra-observer indexes of the NO in the 3 samples (A%: 70±5%; CK: 47±9%; AC: 43±0,7%) were similar or even higher than the observed in EOs (EO1: A% : 63±6%; CK: 42±10%; AC: 36±29%; EO2: A%: 60±7%; CK: 33±12%; AC: 40±3). Interestingly, different samples generated different agreement indexes: for example, EO1´s performances for V1 (A%=66%; CK=50%; AC=32%), V2 (A%= 71%; CK=37%; AC=53%) and V3 (A%=51%; CK=33%; AC=21%) were not similar. Observer's performances were not homogeneous throughout the various behavioral categories: for example, the OE2 showed a mean A% of 8,8±2,8% for swimming and of 33,6±3,7% for immobility in the 3 sample videos. Furthermore, we observed indexes of confusion (or disagreement) between "Swimming" and "Immobility" behaviors in all observers (Swimming A%: V1 [10±5%], V2 [4±2%], V3 [0,2±0,2%]; Immobility A%: V1 [29±9%], V2 [30±6%] , V3 [35±1%]; %D of Swimming/Immobility: V1 [21±6%], V2 [9±3%], V3 [6±2%]). The percentage of disagreements was calculated by adding the Swimming/Immobility and Immobility/Swimming disagreements of each observation, on the total samples.

Conclusion: Contrary to the common believe and practice, human observers are not 100 % reliable sensors of animal behavior. Our data indicated that NO reached an equal or greater level of intra-observer agreement than the OEs, suggesting that the experience in observational studies is not synonymous of reliability in the gathering of data. Thus, expressions as "trained" or "experienced observer", in use to qualify observers in the literature [2], are apparently unreliable. Furthermore, reliability of the rating varies for the behavior being observed and yet unknown properties of

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the sample. The behaviors that obtained the highest percentages of disagreement were Swimming in relation to Immobility and vice-versa. Since frequency and duration of these behaviors are crucial to the understanding the test's outcome, the impact of these variations in reliability must be assessed by test-retest agreement procedures and appreciated, for each behavior and for the whole animal sample, as factors potentially affecting the replicability of FST results.

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Poster

The use of reliability metrics for observational studies in rats submitted to the Forced Swim Test (FST): a systematic review.

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Background: We are planning to develop a tool to help to estimate intra- and inter-observer reliability for behavioral testing such as the forced swimming test (FST) or other tasks requiring direct observation by humans. Theoretically, the higher the intra or inter observers reliability the higher the precision of the measure and consequently, higher the quality of the results. In the present work, we intend to identify the indexes currently used estimate intra- and inter-observer reliability in the FST.

Objectives: This study aims to perform a systematic review to identify and appraise existing reliability tests in observational studies involving the Forced Swimming Test in rats, in addition to the protocol used by the observer and his training.

Methods: We searched for research articles in a database of 2920 articles, created to the meta-analysis of antidepressant effects in the FST [1]. From this library we selected randomly 340 articles (sample size calculated to provide a confidence level of 95%, and a margin of error of ± 5%; www.surveysystem.com/sscalc.htm). Only original research articles (no reviews) reporting the use of rats in FST were included in the systematic review. From the relevant studies the following data were extracted: keywords, date of publication, description of the observational method, type of intra- and/or inter observer index used and the justification for the use.

Results: Two articles reported the use "correlation" as an index of intra-observer estimation without further justification. One study reported the use of a "percent agreement test" based on the frequency of observations. Twenty-three publications (6,7%) reported that FST data was retrieved by "trained observers" failing to specify details of their experience or training. In 79 articles (23,2%), it was mentioned that "a blind observer was used in the experiment to reduce observational bias". When the use was reported, methodology and results were not described and normative references such as [2] were not cited. The studies saying "observers were blinded to reduce observational bias" failed to explain how trainings were performed or assessed. From all articles, 291 (85,5%) were published after the publication of normative protocol by [2], but none of them mentioned it.

Conclusion: Present data indicate little concern with the use, or the report of the use, of the indexes for intra- or inter- observers' reliability in the FST. We suggest the use of reliability indexes (such as Kappa [3]) to estimate inter- and intra-observer agreement for FST and other behavioral models based on direct human rating, which would help to improve the reproducibility in the field.

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Poster

Vertical Climbing: measuring the motivation of rats in an effort task

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Introduction: Motivation deficit is closely related to depressive symptoms. Behavioural tests may be useful to evaluate those psychopathologies symptoms. In basic research, a paradigm to estimate motivation in experimental settings consists of the association of a punishment or a reward to a task that a subject has to accomplish. Punishments often reduce the frequency of the actions taken by the subjects while rewards increase them. In laboratory rodents, efforts to accomplish a task increase proportionally to the increase of the reward [1]. The present work aims to develop a new method to estimate the motivation in

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laboratory rats. For this, the vertical climbing task, often used to rodent resistance training, was adapted from [2] to measure the amount of effort a rat would make to reach a "hedonistic" goal.

Methods: In this preliminary study, adult Wistar rats (male, CEUA-UFSC, number 8080160217), individually placed in a plastic box positioned on the base of a metallic ladder, which led to a shelter on an upper platform containing or not a positive incentive (Froot Loops, FL). Rats were allowed to explore the apparatus freely or forced to climb up the leader (forced group, F). Behavioural trials were videotaped for further analysis with the aid of the Ethowatcher [3] to register parameters (latency, frequency and duration) of exploration of the box (distal, proximal), exploration of the ladder (touching, climbing) and the platform during 5 minutes. In the two first trials (ambientation) there were no incentives on the platform. In the trials three to six (training) there were incentives on the platform, and the height of the base box was higher in the first sessions. Testing trials (seven, without FL; eight with FL) were performed to verify the effectiveness of training.

Results: Regardless of the trial, the box at the base of the ladder was the most exploited environment by rats of any experimental group (Control (E), n=3; F, n=3; FL, n=4), over the course of the session rats tend to explored also the ladder. Rats moved across different behaviors more often (total frequency) in red light (29.4+2.3) than with white light (21.7+1.7). Rats of all groups spent less time only "touching" the ladder after training (27±3,1 s to 16±3 s) while the time spent in climbing the ladder increased (4,4±2,3 s to 12,7±4 s). All rats climbed the ladder at least once but, only six of them reached the shelter (2 E, 4 FL).

Conclusion: In summary, few rats climbed the ladder spontaneously before training. Forcing the climbing seems not to be a negative reinforcement since, in this condition, rats failed to learn to climb the ladder. Froot loops seem to be a positive incentive since its presence increased the frequency of climbing the ladder. Experiments to confirm the present results are in course**.**

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Poster

Evaluatuion of Mice Limbic Brain Areas in the Modulation of Rat Exposure Test-Evoked Response

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Background: Background: Stressful stimuli, such as predator exposure can provoke behavioral response related to anxiety disorder. Rat Exposure Test (RET) is a model that allows assess defensive behaviors in mice since rat is its predator. Limbic system, responsible for emotion control, is composed by some brain areas that modulate defensive behaviors. In this study, in the experiment 1, GABA receptor antagonists, muscimol, GABA A and baclofen, GABA B (MB) were microinjected into the periaqueductal grey (PAG), amygdala (AMY) and hippocampus (dorsal, DH and ventral, VH) in order to evaluate their function in behavioral response elicited by RET exposition. Besides, in the experiment 2, it was assessed the expression of Fos protein, a neural activity marker, after once (sin) or repeated (rep, five times) exposition to RET.

Objectives: Objective: verify the role of brain areas in modulation of response in RET

Methods: Methods: Exp 1: male Swiss mice were exposed once, during ten minutes, to a Long Evans rat, previously microinjected with MB (M: 0,06nmol/0,1µL, B: 0,6nmol/0,1µL) unilaterally into the dorsal PAG (dPAG), or bilaterally into the AMY, VH or DH, through a guide cannula, after stereotaxic surgery and recovery period. Control (ctrl) received saline. Exp 2: mice were exposed, during ten minutes, to a real or a plush (toy) rat once or repeated, in intercalated days. Ctrl were not exposed. After experiment, animals were prepared for Fos immunohistochemistry in dPAG, basolateral (blAMY) or central AMY (cAMY), VH or DH. UFU ethics committee (100/14, 107/15) accepted all protocols.

Results: Results: Exp 1: Student t Test revealed MB intra-dPAG increased time spent on unprotected area (UA) of the TER (ctrl:341.8±68.5;MB:531.3±33.0;$p<0.05$) and decreased time of stretched attend posture (SAP;ctrl:13.4±5.1;MB:5.6±1.9;$p<0.05$). MB into the VH, but not DH, also increased time spent on UA (VH:ctrl:349.1±67.4;MB:520.0±37.1;$p<0.05$ and DH ($p>0.05$). Regarding AMY, no difference was found ($p>0.05$). Exp 2: ANOVA showed increased Fos protein expression on dPAG in both groups sin (ctrl:294.6±9.5;toy:283.74±10.1;rat:851.4±23.8;$p<0.05$) and rep (ctrl:551.0±15.6;toy:571.2±6.2;rat:1106.48±12.2;$p<0.0$

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5) exposed to Rat compared to respective toy and ctrl groups. ANOVA revealed an augment in Fos protein expression on VH in both groups sin (ctrl:111.4±5.3;toy:137.0±7.0;rat:355.1±23.3;p<0.05) and rep (ctrl:124.5±6.3;toy:173.6±8.3;rat:337.0±16.6;p<0.05) exposed to Rat compared to respective toy and ctrl groups. ANOVA showed a decrease of Fos expression in DH at group rat repeatedly exposed compared to rep toy (ctrl:220.9±22.1;toy:263.0±29.2;rat:165.0±11.5;p<0.05). No difference was found in blAMY Fos expression, although same test revealed a decrease in Fos protein expression on cAMY in both toy and rat repeatedly exposed (ctrl:1949.2±194.0;toy:1505.2±58.0;rat:1135.8±88.0;p <0.05) groups compared to ctrl group.

Conclusion: Conclusion: dPAG, VH, but not DH, and cAMY, but not blAMY, seems to play important role in defensive responses exhibited by mice exposed to TER. Moreover, repeated exposition, looks like induce an adoptive response since Fos decreased in central amygdala which needs additional studies.

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Poster

N-Methyl-D-Aspartate Injected Into The Dorsal Periaqueductal Gray Induces Emotional Sensitization And Facilitates The Acquisition Of Contextual Fear Memory

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Background: Aversive memories result from traumatic experiences. Evidence suggest that the encoding of aversive association is facilitated by previous stress [1], resulting in long lasting memories. Dorsal periaqueductal gray matter (dPAG) chemical stimulation (N-methyl-d-aspartate, NMDA) induces the expression of overt defensive behavior (DB) [2] and serves as unconditioning stimulus supporting fear conditioning to neutral odor (CS), as shown by DB elicited by CS exposure in a novel context [3]. NMDA injected into dPAG induces a negative emotional state that potentiates freezing at recall of a contextual fear memory (CFM) trace, 24 hours after training. Few studies investigated the stimulation of brain areas critical for fear expression as sensitizers in fear learning.

Objectives: In the present study, the hypothesis that NMDA intra-dPAG could potentiate CFM performed the day after was tested.

Methods: Rats received NMDA intra-dPAG 24 hours before a weak training, of an association of 1 mild footshock and the context. Systemic injection of cycloheximide (CHX, protein synthesis inhibitor) was applied after dPAG stimulation session or before reexposure to shock-associated context.

Results: Freezing was increased in NMDA-rats immediately after shock suggesting a sensitized DB; also in a retrieval test performed in the context associated to shock. This effect was still observed in a reexposure to associated context 7days after training, suggesting the formation of a long-term aversive contextual memory. CHX injected after dPAG stimulation session impaired the increased freezing in reexposures do context associated to shock. CHX systemic injection before retrieval session in associated context impaired the expression of increased long-term freezing. The impairment in long-term memory expression was also observed when subjects were exposed to a novel context during the retrieval session. However, when a neutral odor was associated to dPAG-stimulation experience, and later reexposed in the neutral context during retrieval session, the long-term contextual memory associated to shock was maintened.

Conclusion: These data suggest that the retrieval session is a critical step in the maintenance of contextual fear memory acquired under dPAG NMDA-stimulation influence. Moreover, the association of both the aversive experiences, i.e., dPAG stimulation, electrical footshock and retrieval, is a process dependent on protein synthesis.

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Oral

Endocannabinoid Modulation Of Dopaminergic Behaviours

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Background: The endocannabinoids and cannabinoid receptors modulate the mesolimbic dopaminergic pathway, with potential implications for biological mechanisms related to psychosis and drug addiction.

Objectives: The aim of this research is to test the working hypothesis that CB1 and CB2 receptors modulate the behavioural responses to dopaminergic drugs in experimental animals.

Methods: Male Swiss mice received systemic injections of cannabinoid-related drugs followed by cocaine, and were then tested in behavioural models related to psychosis and addiction.

Results: CB1 receptor antagonists and CB2 agonists prevent cocaine-induced hyperlocomotion and conditioned place preference in mice. CB2 receptor

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antagonists reverse the inhibitory effects of CB1 antagonists in cocaine-induced responses.

Conclusion: CB1 and CB2 receptors work in concert with opposing functions to modulate psychosis- and addiction-related effects of cocaine.

Poster

Effects of inosine on oxidative stress parameters and acetylcholinesterase activity in the hippocampus of rats submitted to an experimental model of Alzheimer's disease

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Background: Alzheimer's Disease (AD) is the major cause of dementia in the world. Several factors have been associated with the development of this pathology such as oxidative stress and deficits in cholinergic signaling [1], [2]. Inosine is a metabolite derived from adenosine that has important neuroprotective effects [3].

Objectives: Therefore, the objective of this study was to evaluate the effect of inosine treatment on oxidative stress parameters and acetylcholinesterase (AChE) activity in hippocampus of rats submitted to an experimental model of AD [4].

Methods: Male Wistar rats were divided into three experimental groups: I - Control, II - Streptozotocin (STZ) and III - STZ + Inosine (50 mg/kg). The experimental model of AD was induced in animals by intracerebroventricular administration of STZ (3 mg/kg). Three days after the surgical procedure, the animals were treated with inosine (50 mg/kg) intraperitoneally for 25 days and subsequently submitted to euthanasia. The hippocampal activities of the enzymes AChE, superoxide dismutase (SOD) and catalase (CAT) and the levels of reactive oxygen species (EROS), nitrite and thiobarbituric acid reactive substances (TBARS) were evaluated

Results: The administration of STZ increased EROS and nitrite levels and increased AChE and SOD activities while decreased CAT activity in the hippocampus of rats. Inosine treatment was able to prevent all these changes. No changes in total thiol content were observed in any of the groups evaluated. Treatment with inosine did not prevent the STZ-induced increased TBARS levels in hippocampus.

Conclusion: These results demonstrate that inosine was able to prevent biochemical changes in the hippocampus in an experimental model of AD, thus reinforcing the potential of this molecule for the treatment of neurodegenerative diseases.

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Poster

Spatial and discrimination memory impairments exhibited by low-density lipoprotein receptor (LDLr) knockout mice are associated with molecular synaptic changes

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Background: Cholesterol plays a key role in cellular signaling and communication in the central nervous system (CNS). Although it's the organ richest in cholesterol, the synthesis of cerebral cholesterol is completely independent of the periphery, being the astrocytes the cells mainly responsible by this production. The cholesterol secreted by the astrocytes is internalized by the neurons through the low density lipoprotein (LDL) receptor or by the LRP1 (LDL receptor-related protein). Its free fraction is destined to several functions especially in the formation of lipid rafts and synaptogenesis, an event involved in formation of new memories. However, some metabolic disorders present defects in the gene encoding the LDL receptor, such as familial hypercholesterolemia (HF). Growing evidence in the literature has shown that patients with HF also have cognitive impairment and memory loss, which seem ageing-independent. Our group have been demonstrated that LDL receptor knockout (LDLr -/-) mice, a HF genetic model, show memory impairment associated with hippocampal oxidative stress and mitochondrial dysfunction [1,2].

Objectives: In this study we further investigated the behavioral deficits of LDLr-/- mice in memory tasks and the pre and postsynaptic protein profile in pre-frontal cortex and hippocampus, both in male and female.

Methods: Male and female C57BL/6 and LDLr-/- mice (3-4 months) were used (Ethics Committee Protocol-PP00948). To evaluate the spatial and discrimination memories were addressed in the modified Y maze and object recognition test. The locomotor activity was addressed in the open field. Post¬synaptic density pro¬tein 95 (PSD-95) and

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synaptophysin-1 immuno¬content was analyzed by western blot.

Results: No significant locomotor differences were observed in males or females in the open field apparatus. In the object relocation task, a selective deficit of short-term discrimination and spatial memory in female [n=5-8, Factorial ANOVA, F(1, 27)=4.57, p=0.041]. LDLr-/- mice, it was observed. In males it was not possible to detect this parameters, since the wild type animals didn't discriminate the relocated object. On the other hand, in the modified Y maze test, both female and male LDLr-/- mice presented a spatial memory impairments, which was demonstrated by the decreased in time of exploration of new arm [n=7-12, Factorial ANOVA, F(1, 36)=12.193, p=0.001] and in the index of discrimination in the new arm [n=7-12, T-Test, T=3.3 p= 0.006 males; T=2.56 p=0,04 females]. No significant differences were showed in the immuno¬content of synaptophysin-1, in pre frontal cortex and hippocampus, in males or females. However, in the immunocontent of PSD-95, it was observed an increase only in hippocampus of male and female LDLr-/- mice, [n=4, Factorial ANOVA F(1, 12)=8.0785, p=0.014], but not in pre frontal cortex.

Conclusion: These findings reinforce the notion of the development spatial memory impairments in hippocampal-dependent tasks. More importantly, this study provides the first evidence of the existence of the synaptic changes observed in LDLr-/- mice.

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Poster

Treatment with an ethyl-acetate fraction (EAF) of Trichilia catigua (catuaba) alleviates the memory impairment caused by global cerebral ischemia in rats

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Background: Introduction: Popular preparations of Trichilia catigua has been used in Brazil and it has shown a potent in vitro antioxidant activity and a neuroprotective effect in an in vitro model cerebral ischemia. Cerebral ischemia / reperfusion (I / R) leads to severe neuropsychological deficits that are extensively associated with oxidative stress, inflammation and neurodegeneration. We reported previously that a fraction of ethyl acetate (FAE) from T. catigua when given 1 hour before and 4 hours after TGCI reduced cerebral ischemia-induced learning and memory deficits and antioxidant and anti-inflammatory activities.

Objectives: We aimed to investigate whether the ethyl-acetate fraction (EAF) of T. catigua can attenuate the loss of memory caused by TGCI in rats and its action on oxidative stress when administered after 4h of (I/R).

Methods: Methods: In a first experiment the EAF or vehicle was administered for 7 days after and first dose given at 4h to ischemia. Retrograde memory was assessed up to 21 days after TGCI and expressed by three parameters: (i) latency to complete the task, (ii) number of reference memory errors and (iii) number of working memory errors. In a second experiment EAF was administered 4 hours after to ischemia, and antioxidant status was subsequently measured after 24 h of reperfusion. This protocol had the approval of internal Ethical Committee (CEUA nº 7481261017).

Results: Results: Transient, global cerebral ischemia (TGCI, 4-VO) caused the rats to spent more time (latency) to complete the task, and to commit more reference and working memory errors (F) 3,139=6.69-18.13; p <0,0001 vs Sham), indicating they forgot the task that was learned prior to ischemia. The treatment with T. catigua EAF significantly decrease all the three (F4,34= 4.11-13.59; p <0,05 - 0,0001), indicating a memory-protective effect. In the analysis of oxidative stress, TGCI strongly reduced levels of antioxidant enzymes and increased the concentration of carbonylated proteins (F4,34=14.87; p< 0.0001). EAF was able to reestablish the levels of antioxidant enzymes and markers of oxidative damage. EAF.

Conclusion: Conclusion: These findings support the potential role of EAF of Trichilia catigua to ameliorate the cognitive impairments following TGCI in rats. The long-term protective effects of EAF may involve decrease of oxidative stress. Acknowledgments: Financial support CAPES and CNPq.

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Poster

Comparison of adverse events of valproate sodium 300 mg tablet coated under fasted conditions and fed after oral administration

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Background: Sodium valproate is a medicine indicated for the treatment of epilepsy and seizures [1]. After absorption, valproic acid dissociates into the valproate ion in the gastrointestinal tract. Its mechanism of action has not been established, but its activity appears to be related to increased levels of gammaaminobutyric acid (GABA) in the brain. The evaluation of the speed and extension of formulations containing sodium valproate is extremely important, as it will contribute to the development of formulations that have the same bioavailability as the reference product, thus ensuring product interchangeability without therapeutic safety.

Objectives: Evaluation of adverse events in the oral administration of sodium valproate in fasted and fed conditions.

Methods: A phase IV clinical study was performed employing 28 healthy volunteers who received valproate after a minimum of 8 (eight) hours of fasting. In addition, the study was carried out using 37 healthy volunteers, and the product was administered after standardized breakfast. Both studies were delineated in a 2 x 2 design in which the research participants received valproate in both periods, with one being administered the generic candidate, called test, and in another the reference formulation. In order to guarantee the proper execution of the experiment, the diet, evaluation of vital signs and all procedures performed during hospitalization were standardized and performed according to a clinical protocol duly approved by the Research Ethics Committee.

Results: During the study in the fasting condition, there were 18 non-serious adverse events, 44% unrelated, 16% suspected and 40% related to the drug studied. During the study in the feeding condition, 13 non-serious adverse events were observed, 23% unrelated, 77% suspected and more related to the drug studied.

Conclusion: The events that have a relationship with medicine were not studied in fasting were headache and diarrhea. Among the events that began in the food study, with the relation with the administered drug, the main ones referred to diarrhea, headache and soft faeces. The drug was well tolerated by the participants, with no adverse events and no improvement in monitored vital signs, which is an oral health test, regardless of the patients' support condition.

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Poster

Bilateral Injection of 6-Hydroxydopamine Into The Dorsolateral Striatum of SHR and SLA16 Rats

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Background: SHR and SLA16 isogenic rats are genetically identical except for a chromosome 4 region. This region includes anxiety-related response 16 (Anxrr16), a quantitative trait loci that is critical to the expression of anxiety-like and learning/memory behavior in rats [1-2]. An important role of dopamine (DA) neurotransmission is hypothesized, but several behavioral and neurochemical aspects of these strains are yet not clear [2]. A recent study showed that SLA16 rats are more prone to develop oral dyskinesia than SHR rats (unpublished data), a fact that is thought to be closely related to DA-ergic transmission in the dorsal and ventral striatum [3].

Objectives: Here, we aimed to investigate a putative differential susceptibility of SHR and SLA16 rats to a cathecolaminergic neurotoxin 6-Hydroxydopamine (6-OHDA) that is widely used to induce motor, cognitive and emotional impairment in rats [4].

Methods: Forty SHR and SLA16 rats were divided in control or 6-OHDA-lesioned groups (n=10 animals per group). Lesioned animals received a bilateral injection with 6-OHDA (10 µg/hemisphere) into the dorsolateral striatum. The control group was injected with vehicle solution. All animals received a prior injection of desipramine (20 mg/kg, i.p.) to protect noradrenergic terminals against 6-OHDA uptake and toxicity.

Results: SLA16 rats displayed higher locomotor activity than SHR in the open field test, regardless of treatment. The 6-OHDA reduced the time spent in the open arms of the elevated plus maze. Overall, no other significant strain or treatment effects were found in motor parameters addressed on the rotarod, activity cage, catalepsy bar test, adhesive removal test, grip test and wire hanging test.

Conclusion: SHR and SLA16 showed contrasting behavior in the open field test. This result further corroborates the phenotypic impact of the genomic region comprising Anxrr16. The 6-OHDA caused anxiogenic effects in the elevated plus maze and we did not find any evidence for 6-OHDA-induced motor impairment in SHR or SLA16 rats. Therefore, reduced motor capacity should not act as a confounding factor in cognitive and emotional assessments like the open field test.

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Poster

Do genetic variations of the NLRP3 gene interfere in interleukin-1β levels and Major Depressive Disorder diagnosis?

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Background: The inflammasome NLRP3 is a protein complex responsible for processing the pro-forms of interleukin-1β (IL-1β) and interleukin-18 (IL-18) into their active forms. Recently, increased expression of NLRP3 complex proteins was found in peripheral mononuclear cells of Major Depressive Disorder (MDD) patients, increasing the interest of understanding the role of this protein complex in the pathophysiology of this disorder.

Objectives: Evaluate the effect of a single nucleotide polymorphism (SNP) in the NLRP3 gene (rs10754558, C/G) on levels of IL-1β and MDD diagnosis.

Methods: A cross-sectional population based study was conducted and our sample for this experiment included 161 individuals (83 controls and 78 individuals with MDD). Blood samples from patients diagnosed using the Mini International Neuropsychiatric Interview 5.0 according to DSM-5 criteria and from the control were collected. DNA was extracted from blood leukocytes and genotype was performed by qPCR. Serum IL-1β levels were measured by ELISA. The study was approved by Human Research Ethics Committee of Catholic University of Pelotas (2010/15).

Results: In our sample, subjects with GG genotype had higher IL-1 levels when compared to CC subjects. No differences were found in the peripheral levels of IL-1β in MDD patients and controls. However, when we evaluated the interaction between genotype and diagnosis on the levels of IL-1, the results indicated that MDD subjects carrying GG genotype had higher serum levels of IL-1 when compared to CG (p=0.01) and CC (p=0.05) subjects with MDD and with subjects without MDD.

Conclusion: These results further support the notion that the GG genotype of this SNP in NLRP3 gene (rs10754558) is associated with gain of function. Additionally, this function is even exacerbated in patients with MDD. The presence of inflammation in patients with MDD is heterogeneous and the identification of potential genetic markers controlling inflammatory responses might be useful not only as a differential biomarker to characterize heterogeneity in diagnosis, but also as a potential new target for pharmacological intervention in specific groups of patients.

Poster

Object recognition and contextual fear memoryimpairments exhibited by young adult low-density lipoprotein receptor (LDLr) knockout mice are not associated with hippocampal atrophy

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Background: 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 [1]. Previous studies using LDLr knockout (LDLr-/-) mice have demonstrated learning and memory impairments accompanied by neurochemical and neuromorphological changes in the hippocampus [2,3].

Objectives: In this study we further investigated alterations in the performance of LDLr-/- mice in hippocampal-dependent memory tasks andputative changes inhippocampal volume.

Methods: Male C57BL/6 and LDLr-/- young adult mice (3-4 months) were used. The experiments were performed after approval of the protocol by the Ethics Committee of the Institution (PP00948).To ensure the model validity, the serum cholesterol concentration was evaluated. The locomotor activity was addressed in the open field. To evaluate memory parameters, the short-term recognition and long-term contextual fear memories were addressed in the object recognition and fear conditioning tasks, respectively (N=8-10). The hippocampal volume was determined after hematoxylin eosin staining by the Cavalieri's principle.

Results: A three-fold increase in serum cholesterol concentration was observed in LDLr-/- animals (80mg/dL to 234 mg/dL). No significant locomotor differences were observed between genotypes in the open field apparatus. In the object recognition task, it was observed a memory deficit of short-term recognition memory [T-Test, t= 1.050, p= 0.328, in relation to 50%] in LDLr-/- mice. Likewise, in the fear conditioning tasksLDLr-/- micepresented long-term

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contextual fear memory impairments [One-way ANOVA, F (1, 20) =11.316, p=0.00309]. Although the cognitive impairment no significant differences were showed in the hippocampal volume between genotypes [T-Test, t= 1.288, p= 0.287, between groups].

Conclusion: These findings reinforce the notion of the development of learning and memory impairments in hippocampal-dependent tasks. More importantly, this study provides the pioneering evidence that, at least in young adult mice, these cognitive impairments are not associated to hippocampal atrophy.

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Poster

Impact of stress during pregnancy on child development: role of hypothalamic-pituitary-adrenal axis activation

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Background: Stress response is a coordinated reaction that occurs as a function of aversive stimulus, which activates the sympathetic division of the autonomic nervous system and leads to the release of cortisol (a glucocorticoid steroid hormone) by adrenal glands [1]. When released into the bloodstream, cortisol acts throughout the body mobilizing energy reserves and promoting immunosuppression, thereby preparing the individual to cope with the various life stressors and contributing to the body's physiological response to stress. Stress experienced by woman during pregnancy may have a significant impact on the development of the baby's brain, by affecting the volume of hippocampus or amygdala, causing changes in emotional systems of the child. Chronic exposure to stress, as domestic violence situations or intense work, can cause long-term reduction in activity of special placenta enzymes that normally prevent the cortisol to cross placenta reaching the fetus [2]. Babies exposed to mother´s stress hormones during pregnancy are born more irritable and are more likely to cry; they also have increased behavioral responses to stress. Amygdala exposed to high levels of cortisol during development period, especially early in pregnancy, can become more responsive. In cases of exposure to prenatal stress, amygdala can have an increase around 6% in volume [2]. A cognitive study combined with a structural magnetic resonance, showed that higher levels of stress were associated with a decrease in hippocampal volume in adolescence [3]. This study provides empirical evidence of how experience can shape brain development, but thanks to brain plasticity it's possible to interfere and prevent negative consequences. The hypothalamus plays a key role in motor-visceral, somatic-motor and humoral responses, mediated by hypothalamic-pituitary-adrenal (HPA) axis [4]. Amygdala activation stimulates HPA axis and the stress response, whereas hippocampus exerts an inhibitory control. Human babies have a plastic brain, able to shape throughout life, as many regulatory systems are still under development. There are good chances to recover these systems through psychotherapy, by remodeling synapses, and positive experiences, building a healthy and secure attachment bond during the first years of life, enabling the hippocampus affected by stress to recover its normal volume.

Objectives: In the present study, the analysis of the impact of stress during pregnancy on child development enables to find forms of intervention and prevention of maladaptative responses.

Methods: A review highlighting the structures and hormones involved in the stress response, their effects on the body and the impact of prenatal stress on child development.

Results: Human brain neuroimaging studies demonstrate a decrease in hippocampal volume in people who have been exposed to stress. The continuous exposure to cortisol can lead to dysfunction and death of hippocampal neurons.

Conclusion: The impact of long term exposure to stressful situations is deleterious and can result in increased blood pressure, damage to muscle tissue, inhibition of inflammatory responses and immune system suppression. Prenatal stress exposure also leads to changes in brain´ structure, which in turn can result in inadequate coping strategies as response to stressors. Based on brain plasticity idea, it's possible to interfere with with psychotherapy, by remodeling synapses and preventing maladaptative responses.

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Poster

Effects of Environmental Enrichment on Depressive-like Behavior and Hippocampal Neuroplasticity in a Model of Huntington Disease

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Background: Huntington's disease (HD) is a genetic neurodegenerative disorder characterized by motor, neuropsychiatric and cognitive deficits. It is caused by an abnormal expansion of the CAG tract in the huntingtin gene [1]. The YAC128 mouse model of HD exhibits motor abnormalities, cognitive dysfunction and neuropsychiatric symptoms, which are similar to the human disease [2]. The environmental enrichment (EE) is a condition where animals are exposed to high stimulation compared to conventional housing conditions. Rodents housed in EE show significant changes in brain biochemistry, synaptic morphology, and neuronal function compared with standard-housed animals [3].

Objectives: The objective of this study was to determine if EE exposure, for 60 days (2-4 months) has positive effects on depressive-like behavior and hippocampal cell proliferation in the YAC128 HD mice.

Methods: In this study, 2 months old male and female wild-type (WT) and YAC128 mice (n=6-10) were exposed to EE for 2 months or to standard housing conditions. At the end of this period, depressive-like behavior was assessed using the tail suspension test. 24h after behavioral test animals were perfused with 0.9% NaCl followed by 4% paraformaldehyde. Brain serial coronal sections were obtained on a vibratome at 30µm thickness. Cell proliferation in the hippocampal dentate gyrus (DG) was assessed, performing immunohistochemistry for the endogenous proliferation markers Ki-67 and proliferating cell nuclear antigen (PCNA) and neuronal differentiation using the Doublecortin (DCX). The total number of immunoreactive cells was counted and the results were analyzed using two-way ANOVA. Further, dendritic arborization was evaluated by Sholl analysis using DCX labeled neurons and the results were analyzed by repeated two-way ANOVA.

Results: EE increased Ki-67 positive cells ($p < 0.05$) in the WT mice. Exposure to EE decreased the number of DG-Ki-67 positive cells ($p < 0.05$) and reverted the depressive-like behavior to WT level in the YAC128 mice. There were no differences in the number of DG-PCNA positive cells among groups. EE increased the differentiation in WT and YAC128 mice ($p<0.01$). Dendritic arborization was also increased by the EE exposure in WT mice, the maximum distance reached by the immature neurons ($p<0.01$), and the total number of dendrites intersections in the Sholl analysis were increased ($p<0.05$) when compared to the WT group housed in a standard housing condition.

Conclusion: Our results confirmed that exposure to an EE is able of modulating hippocampal neuroplasticity in WT mice and YAC128 mice. EE may play a potential therapeutic role in the treatment of neuroplasticity deficit that occurs in DH.

EP acknowledges the support given by CAPES. Correspondence to: eveliniplacido@gmail.com

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Poster

Behavioral And Neurochemical Changes In Mice Adulthood Induced By Early Life Stress

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Background: Background: Stress is an adaptive response that performs physiological changes in the face of aversive situations. However, when intense or prolonged, or even during critical development periods, stress can elicit neurochemical and neuroanatomical changes that negatively impact on brain functioning. Childhood stress caused by parental neglect, physical or emotional disturbances, may lead to psychiatric disorders in adulthood. Neuroinflammatory processes have been associated with mechanisms of vulnerability and resilience to stress. In this sense, the NLRP3 inflammasome is a protein complex activated after stress and responsible for maturation and release of interleukin-1β (IL-1β) and innate immune response.

Objectives: Objectives: This study aims to investigate neuroinflammatory mechanisms and behavioral changes caused by early stress and its impact on adulthood.

Methods: Methods: 30 days-old female Swiss mice were subject to early stress protocol (ES) that consisted in a single episode of restraint stress for 7h followed by a single administration of lipopolysaccharide (LPS, 0,83mg/kg, i.p.) 24h later. Twenty-four hours (childhood) or 30 days (adulthood) after LPS administration, the animals were submitted to behavioral tests. Depressive-like behavior was evaluated with the forced swimming test (FST), the locomotor activity was evaluated with the open-field test (OFT), the anhedonic behavior with the sucrose splash test (SST), and the working memory with the Y-maze test (YMT). After behavioral analysis, western blot and ELISA evaluated the immunocontent of NLRP3 and IL-1β, respectively, in the hippocampus

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(HPC) and nucleus accumbens (NAcc) (CEUA protocol 9242221018).

Results: Results: Mice submitted to early life stress and evaluated after 24h, at 30 days of age, we observed impaired locomotion in the OFT, but no changes in depressive-like behavior, anhedonia or memory performance. On the other hand, animals submitted to early-life stress and evaluated after 30 days, at 60 days of age, presented a depressive-like behavior in FST, with no other behavioral changes. The neurochemical analysis showed an increase in the hippocampal NLRP3 immunocontent 24h after early-life stress that was not persistent through adulthood. However, IL-1β levels in the HPC and NAcc were not increased 24h after early-life stress, but reduced levels were found in both control and early-life stress mice evaluated at adulthood.

Conclusion: Conclusion: We conclude that a single early-life episode of psychological stress combined with physical stress is capable of inducing long-term behavioral changes. The activation of NLRP3 inflammasome pathways might trigger the early-onset mechanisms involved in the long-term behavioral changes, but more studies are needed.

Poster

The use of antidepressants in the primary care: profile of users in a Municipality in the West of Santa Catarina

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Background: Background: Many studies in different countries show that depression and other psychiatric disorders, such as anxiety, are mostly treated in primary care. In Brazil, there are few reviews studying the profile of consumption of antidepressant drugs in Primary Care by the population, so it is important to know the profile of those users, the prescribers, which pathologies are being used and if their use is given appropriately.

Objectives: Objectives: To characterize the profile of the patients using antidepressant drugs in the Public Health Service of a municipality in the West of Santa Catarina and compare it to other places in Brazil and in the world.

Methods: Methods:To create a profile of the users of the antidepressants in the targeted municipality, semi-structured questionnaires were applied to those patients who accepted to participate in the study. Data were collected in the public pharmacies of Maravilha, Santa Catarina, which carry out dispensing of antidepressant drugs in the year 2016. A systematic review of the literature was performed to outline the theoretical profile of users of antidepressant drugs in Brazil and in other countries.

Results: Results: The users of antidepressant drugs in the municipality were mostly women (89%), over 50 years of age, of low schooling, married or with a partner and have used the drug for a year or more (75%). The most prescribed drugs belong to the class of SSRI and were prescribed in the majority of cases by general practitioners (49%) from the "Sistema Único de Saúde" (Brazilian public health care system) (55%). The most frequent reasons for using the antidepressant, according to the patients, were depression, anxiety, insomnia and pain. Seventy five percent of the patients were under treatment longer than a year, 88% of them report to ignore when the treatment would finish.

Conclusion: Conclusion: The profile of antidepressant users in our sample was consistent with the literature and similar to the results obtained in the systematic review. In addition, the use of these antidepressant drugs tended to be chronic. For this reason, a guideline on discontinuation and non-pharmacological treatments would be helpful to the patients and professionals involved in the process of the treatment. Further studies on long-term treatment with antidepressants are suggested.

Poster

Evaluation of cell viability in culture of astrocytes submitted to treatment with Magnetic Stimulation

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Background: Neurological pathologies are commonly treated with drug therapies. However, alternatives such as non-invasive Brain Stimulation, both electrical and magnetic, have been studied. The researches made with these models show the possibility of this therapy being coadjutant in treatments of diseases such as Alzheimer's, Parkinson's, depression, chronic pain, among others [1,2,3]. Recent studies with animals have been important in identifying the mechanisms by which the cranial stimulation would produce its effects [2,3]. There is evidence that stimulation is not only as a neuromodulator but also as an inducer of neuroplasticity and have neuroprotective effects. During the process of transcranial stimulation, not only pathological cells are affected by the stimulus, but also healthy cells located around them. The effects on healthy cells have not been well elucidated [4]. One cell type that could suffer from this therapy is astrocytes. These cells constitute the most abundant

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glial component in the brain of mammals and together with the fact that it has such functional importance, it justifies research with a focus on this cellular type [5]. The time of exposure to stimulation may also be a factor in determining whether there will be harmful implications for them. An efficient way to verify these hypotheses is to evaluate the viability of them after stimulation in primary culture.

Objectives: The objective of this study was to evaluate the cell viability of astrocytes obtained from primary cultures submitted to treatments with magnetic stimulation at different times.

Methods: This study used the Wistar rat as an animal model and was experimental, in vitro. The animals used were released by the committee of ethics of Federal University of Pelotas under number 4408-2016. The effect of magnetic stimulation on biochemical aspects in astrocyte cell cultures was evaluated. Cerebral cortex of neonatal Wistar rats (one to two postnatal days) was used for this culture following a specific protocol, being cultivated in twenty-four well plates. The cultured cells were maintained in an incubator at 5% CO2 levels and a temperature of approximately 37 ° C. At intervals of three to four days, the cell medium from these cultures was switched. After the cells had reached confluence (20 days after sowing) magnetic stimulation was initiated. The stimulation device used produces a static magnetic field of approximately 305 mT and was designed by the Bioengineering of Hospital de Clínicas de Porto Alegre. The treatments that the cultures received were 5, 15 and 30 minutes of stimulation daily for one week and a plate was maintained for total control. At the end of the last day of stimulation the biochemical analyze (MTT) was performed to verify the cell viability of the cultures.

Results: Cells that were stimulated for 5 minutes showed an increase in cell viability compared to total control (non-stimulated cells cultured on another plate) ($p<0,05$). Cells stimulated for 15 minutes also had an increase in cell viability compared to control ($p<0,05$). However, the cells submitted to 30 minutes of stimulation presented no difference in cellular viability when compared to the control ($p>0,05$). When only the stimulated groups were compared, we observed that there was no statistical difference regarding cell viability between the group stimulated for 5 minutes and the group stimulated for 15 min ($p>0,05$). These two groups had a statistically significant improve when compared to the group that was stimulated for 30 minutes ($p<0,05$ and $p<0,05$, consecutively).

Conclusion: In clinical practice, the use of this stimulation affects both healthy and unhealthy cells. Usually, we expected that will be no reduction in the function on normal cells. If the cells present a decay in cell viability it possible to be deleterious. The magnetic field generated from the device was able to change the viability of the cells in times of small exposure. Based on the results obtained after experimentation, we can infer that short periods of stimulation improve cell viability. Larger treatment times (30 minutes) do not alter this response in astrocytes, and may be considered positive. It could be a sign that their functioning is regular. Following this reasoning, this 30-minute model of cellular therapy for treatment of neurological disorders could be employed without costing the health of healthy cells. It is necessary do more experiments with other periods of stimulation to have a better evaluation about this therapy.

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Poster

Involvement of monoamines in depressive- and anxiety-like behaviors in an animal model of Parkinson's disease

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Background: The dopaminergic neurodegeneration is a hallmark of Parkinson's disease (PD), however the noradrenergic and serotonergic systems are also altered. An impaired serotonergic neurotransmission plays a role in the development of both motor and non-motor disturbances, such as anxiety and depression [1]. According to the Braak staging of PD [2], neuropathological alterations in neurons of the raphe nuclei arise from stage 2, which precede the alterations in substantia nigra compacta (SNc) during the stage 3. Moreover, structures including the amygdala, locus coeruleus, hippocampus and cerebral cortex are compromised prior to nigrostriatal neurons. Studies have suggested that non-motor disturbances are a consequence of dopamine dysfunction concomitant with noradrenaline and/or serotonin alterations, indicating that the neurodegeneration is beyond the dopaminergic transmission in PD [3].

Objectives: The present study aimed to investigate the involvement of monoamines in brain areas related to depressive- and anxiety-like behaviors, and short-term memory in an animal model of PD.

Methods: Male Wistar rats underwent a 10-day protocol used to induce nigrostriatal lesion. One group received rotenone 2.5 mg/kg intra-peritoneally (i.p.), and another group received vehicle (1 mL/kg) i.p. Anxiety-like behavior and short-term memory were

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evaluated on 22 and 25 days after the last rotenone injection, respectively. The animals were also tested in the modified forced swim test 28 days (training session) and 29 days (test session), in order to assess the depressive-like behavior. At the end of the last test, the rats were decapitated, and brains dissected for neurochemical analysis. Data were analyzed using repeated measures ANOVA followed by Bonferroni post hoc test and Student's t test ($p \leq 0.05$). All procedures were approved by the Animal Care and Use Committee of the UFPR (protocol numbers 697 and 1154).

Results: The short-term memory test demonstrated that the rotenone group showed a significant increase in the ratio of investigation (RID) ($p=0.01$) compared with the control group, when the same juvenile rat was re-exposed 30 min after the first exposition, indicating an impairment in the social recognition memory of adult rats. In the modified swim test, a significant increase in immobility time was observed in the rotenone group compared with the control group ($p=0.027$). In addition, a significant decrease in swimming time was observed in the rotenone animals ($p=0.04$), compared with the control. No significant difference in climbing was observed between groups. Anxiety-like behavior evaluation did not indicate a significant difference between the groups, neither in the percentage of open arms entries nor in the percentage of time in open arms. Dopamine levels were found significantly reduced in striatum, prefrontal cortex and amygdala ($p<0.01$). Moreover, dopamine metabolites, DOPAC and HVA were decreased in those structures ($p<0.01$). Noradrenaline and serotonin were decreased significantly in prefrontal cortex and striatum ($p<0.01$). The analysis of these monoamines showed that only noradrenaline was significantly decreased in amygdala of rotenone group compared with the control group ($p<0.01$).

Conclusion: The results indicate that the depressive-like behaviors and short-term memory impairment observed may be related to alterations in monoamines content in striatum and prefrontal cortex.

Acknowledgments: CAPES, CNPq

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Poster

The temporal participation of hippocampal CB1, CB2 and PPARγ receptors in the cannabidiol consolidation impairing effect

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Background: Classically, the memory consolidation time-window is described lasting 6 hours [1] and this process requires proteins such Arc, a product of an immediate early gene [2], and specific brain regions like the dorsal hippocampus (DH) in rodents [3]. Cannabidiol (CBD), the major non-psychotomimetic phytocannabinoid present in Cannabis, has a multimodal mechanism [4] and is able to disrupt fear memory consolidation [5]. However, the temporal time window as well as the mechanisms in the dorsal hippocampus (DH) underpinning these effects are unknown.

Objectives: The objective was to investigate the mechanisms underlying the CBD effects in DH during fear memory consolidation.

Methods: Male Wistar rats (270-320g) with guide cannulas implanted bilaterally in the DH were exposed to a strong contextual fear conditioning (CFC) protocol that consisted of familiarization, CFC (3 footshocks of 1.0mA/3s) and memory retrieval (Test 1), conducted 24 h or 7 days apart. In experiment 1 CBD (10-30 pmol) or vehicle (VEH) were infused 0 h, 1 h or 3 h after CFC into the DH. In experiment 2, 0 h or 1 h after CFC, rats were pre-treated with AM251 (CB1 antagonist; 0.5 nmol), AM630 (CB2 antagonist; 0.1 nmol), WAY100635 (5-HT1A antagonist; 0.14 nmol), ZM241385 (A2A antagonist; 10 nM) or GW9662 (PPARγ antagonist; 32 pmol) and then received VEH or CBD (30 pmol). In experiment 3, rats were treated with VEH or CBD i.p. (10 mg/kg) 0 h or 1 h after CFC and sacrificed for further analysis of Arc protein in the DH. CEUA #1048.

Results: Repeated-measures ANOVA showed significant treatment effect for freezing time at 0 h [$F(2, 19) = 19.167$; $P = 0.00003$] and 1 h [$F(1,18) = 17.978$; $P = 0.00049$]. The CBD infusion (30 pmol) reduced the freezing behavior when compare to control one or seven days later. Two-way ANOVA showed significant interaction effect between pre-treatment and treatment for freezing time at 0 h [$F(5, 97) = 2.5677$; $P = 0.03163$] and 1 h [$F(5, 93) = 3.5080$; $P = 0.00598$]. The CB1 or CB2 blockade totally prevented the CBD effect 0 h after CFC, the 5-HT1A and A2A blockade partially prevented this CBD effect, and the PPARγ blockade did not change the CBD effect. However, after 1 h, only the PPARγ antagonism prevented the CBD effect. Moreover, one-way ANOVA showed treatment effect for Arc expression in the DH at 0 h [$F(2,23) = 13.40$; $P = 0.0001$] and 1 h [$F(2,25) = 4.35$; $P = 0.025$]. The CBD treatment reduced the Arc expression when compared to control.

Conclusion: CBD-induced memory consolidation impairment depends on CB1 and CB2 receptor at 0 h,

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on PPARγ at 1 h and involves the Arc reduction expression, suggesting that the mechanisms controlling the CBD effect in memory consolidation changes along time in the DH.

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Poster

Infusing Muscimol into the Infralimbic Cortex During Contextual Fear Memory Consolidation Increases Generalized Defensive Responses and Hampers Extinction

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Introduction: the formation and maintenance of memories are some of the most important physiological processes for animal behavior regulation. For this processing, several brain regions are required, and their activity can modulate it. In rodents, the infralimbic (IL) cortex is one of these brain regions, having its activity being associated with learning and consolidation of extinction memory [1,2]. However, its role in the acquisition and/or consolidation of contextual fear memories is not fully understood. Thus, the aim of this study was to investigate the IL's role in the acquisition and consolidation of aversive memories in a contextual fear conditioning (CFC) paradigm.

Methods: In our experiments, the GABA-A agonist muscimol (MUS) was injected directly in the IL cortex, through guide cannulae surgically implanted, to transiently inactivate this brain region in different stages of memory processing (acquisition or consolidation). In all experiments, animals were tested in the same context (test A) or in a novel one (test B) in the days following the CFC.

Results: Initially, MUS or vehicle (VEH) was bilaterally injected into the IL 20 min before CFC, interfering with the acquisition of contextual fear memories. On test A, no differences were observed between groups, while in test B, MUS-treated rats expressed a significantly higher freezing level compared with controls, suggesting that activity in the IL during acquisition is necessary for the encoding of specific contextual fear memories. In the second experiment, MUS or VEH was injected into the IL immediately after CFC, to interfere with memory consolidation. As on the first experiment, no differences were found between groups on test A, but on test B the MUS group expressed significantly higher freezing levels when compared with controls. In the next experiment, MUS or VEH was injected into the IL 6 h after the CFC, in a moment in which the consolidation process is considered to have already ended. No differences were found in test B, suggesting the IL involvement is time-dependent. When animals were trained in a lower intensity CFC, the results agreed with those of the first two experiments, indicating that the IL control over consolidation is independent on the conditioning intensity. Finally, the last experiment assessed the effect of an IL inactivation during consolidation over subsequent extinction learning. The results suggest that IL activity during the consolidation of contextual fear memories is necessary for the successful posterior extinction, as MUS-rats expressed significantly higher freezing levels in the post-extinction test A.

Conclusion: The present results suggest that activity in IL cortex during contextual fear memory consolidation controls memory specificity and extinction susceptibility.

Ethics: The research was approved by the local Animal Research Ethical Committee under the protocol number 9263110516

Financial support: National Council for Scientific and Technological Development (CNPq)

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1 Milad, Nature, 420, 70, 2002
2 Do-Monte, J. of Neuroscience, 35, 3607, 2015

Poster

Newly acquired and reactivated contextual fear memories are more intense and prone to generalize after activation of prelimbic

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Background: The formation and maintenance of memories are some of the most important physiological processes for animal behavior regulation. For this processing, several brain regions are required, and their activity can modulate it. In rodents, the infralimbic (IL) cortex is one of these brain regions, having its activity being associated with learning and consolidation of extinction memory [1,2]. However, its role in the acquisition and/or consolidation of contextual fear memories is not fully understood.

Objectives: The aim of this study was to investigate the IL's role in the acquisition and consolidation of aversive memories in a contextual fear conditioning (CFC) paradigm.

Methods: In our experiments, the GABA-A agonist muscimol (MUS) was injected directly in the IL cortex, through guide cannulae surgically implanted, to

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transiently inactivate this brain region in different stages of memory processing (acquisition or consolidation). In all experiments, animals were tested in the same context (test A) or in a novel one (test B) in the days following the CFC.

Results: Initially, MUS or vehicle (VEH) was bilaterally injected into the IL 20 min before CFC, interfering with the acquisition of contextual fear memories. On test A, no differences were observed between groups, while in test B, MUS-treated rats expressed a significantly higher freezing level compared with controls, suggesting that activity in the IL during acquisition is necessary for the encoding of specific contextual fear memories. In the second experiment, MUS or VEH was injected into the IL immediately after CFC, to interfere with memory consolidation. As on the first experiment, no differences were found between groups on test A, but on test B the MUS group expressed significantly higher freezing levels when compared with controls. In the next experiment, MUS or VEH was injected into the IL 6 h after the CFC, in a moment in which the consolidation process is considered to have already ended. No differences were found in test B, suggesting the IL involvement is time-dependent. When animals were trained in a lower intensity CFC, the results agreed with those of the first two experiments, indicating that the IL control over consolidation is independent on the conditioning intensity. Finally, the last experiment assessed the effect of an IL inactivation during consolidation over subsequent extinction learning. The results suggest that IL activity during the consolidation of contextual fear memories is necessary for the successful posterior extinction, as MUS-rats expressed significantly higher freezing levels in the post-extinction test A.

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Poster

Participation of the P2X7-NLRP3 inflammasome pathway in stress susceptibility and antidepressant response in the learned helplessness model

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Background: The way individuals perceive and cope with stressful events can determine resilience or susceptibility to the development of stress-related psychiatric disorders, such as major depression disease (MD). Stress can increase the release of ATP in the central nervous system, leading to the activation of its receptors (P2X and P2Y), being the activation of P2X7 directly related to the activation of the NLRP3 inflammasome cascade. Treatment with P2X7 antagonists induces antidepressant-like effects in animal models, modulating the expression of the NLRP3, caspase-1, and IL-1β, components of the NLRP3 inflammasome cascade. Treatment with antidepressants reverses the effects of behavioral disorders induced by chronic stress, but their effects on P2X7-NLRP3 inflammasome pathway are poorly understood. Therefore, this study investigated if changes in the expression of genes of the P2X7-NLRP3 inflammasome pathway could be associated with stress susceptibility and antidepressant response.

Objectives: To investigate the P2X7-NLRP3 pathway in resistant/susceptible or responsive/non-responsive animals submitted to a learned helplessness protocol and treated with fluoxetine

Methods: After being submitted to the pre-test session of learned helplessness (LH) protocol, 80 male Wistar Hannover rats were treated for 7 days, once daily, with fluoxetine (10mg/kg) or saline. In the 7th day, the animals went through the test session, and the number of failures in escape or avoidance was quantified. The animals were classified into resilient/susceptible (vehicle-treated group) or responsive/non-responsive (fluoxetine-treated group) and the gene expression for P2X7, NLRP3, caspase-1, and IL-1β was quantified by qPCR in the prefrontal cortex (PFC), dorsal and ventral hippocampus. The protocol was approved by the local Ethics Committee (Prot. No.18.1371.60.1).

Results: Exposure to the LH protocol induced helplessness behavior in 65% of the animals (susceptibles, n=11), which presented decreased expression of P2X7 in the dorsal hippocampus in comparison to resilient animals (n=6) (Kruskal-Wallis test; p= 0.05). Surprisingly, only the animals that responded to fluoxetine treatment (responders, n=7) presented decreased expression of P2X7 and NLRP3 in the dorsal hippocampus (Kruskal-Wallis test; p= 0.02 and p= 0.05, respectively) when compared to non-responders (n=9). No alterations were observed in the gene expression of the P2X7-NLRP3 pathway components in the ventral hippocampus and PFC of the resilient/susceptible or responsive/non-responsive animals

Conclusion: Chronic stress was able to induce behavioral changes characteristic of learned

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helplessness associated with decreased P2X7 gene expression in the dorsal hippocampus. Response to fluoxetine was associated with decreased P2X7-NLRP3 gene expression in the dorsal hippocampus, thus revealing that resistance to treatment might be associated with failure to dampen P2X7-NLRP3 activation. Protein analysis are being processed to confirm these results. Taken together, these data points to the complex regulation of purinergic and neuroimmune signalling components of the dorsal hippocampus in stress exposure and in the responsiveness to fluoxetine.

Poster

Antidepressant-like effect of guanosine involves activation of AMPA receptors and BDNF/TrkB pathway

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Background: Guanosine is a purine nucleoside that has previously shown to exhibit antidepressant-like properties. Although the mechanisms underlying its effects are not well establish it was demonstrated that guanosine activates mTOR signaling pathway, similar to the fast-acting antidepressant ketamine. The activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and brain-derived neurotrophic factor (BDNF)/tropomyosin receptor kinase B (TrkB) pathway has been implicated in fast antidepressant responses.

Objectives: Therefore, this study investigated if the antidepressant-like effect induced by guanosine in the tail suspension test (TST) involves the modulation of AMPA receptors, L-type voltage-dependent calcium channels (VDCC), BDNF/TrkB signaling, and its downstrea

Methods: Female Swiss mice were treated with a guanosine (0.5 mg/kg, p.o.) oral vehicle and 45 min after, animals received treatment with 6,7-dinitroquinoxaline-2,3-dione (DNQX) (AMPA receptor antagonist, 2.5 µg/site, i.c.v.), K-252 (TrkB receptor antagonist, 1 µg/site, i.c.v.), BDNF antibody (1 µg/site, i.c.v.) or vehicle. After 15 min tail suspension test (TST) was carried followed by open field test (OFT). In other set of experiments mice were treated with guanosine (0.5 mg/kg, p.o.) and after 30 min they received verapamil (VDCC inhibitor, 10mg/kg, i.p.) or vehicle. After 15 min animals were submitted to the TST and OFT. All procedures were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and experiments were performed after approval of the protocol by the Ethics Committee of the Institution (PP00795 Protocol).

Results: The antidepressant-like effect of guanosine (0.5 mg/kg, p.o.) in the TST was prevented by the administration of DNQX (AMPA receptor antagonist, 2.5 µg/site, i.c.v.), verapamil (VDCC inhibitor, 10 mg/kg, i.p.)., BDNF antibody (1 µg/site, i.c.v.), or K-252a (TrkB receptor antagonist, 1 µg/site, i.c.v.). Increased synapsin-I immunocontent and higher phosphorylation level of p70S6K in the hippocampus was observed 60 min after guanosine administration.

Conclusion: Our results indicate that the antidepressant-like effect of guanosine in the TST may be dependent on the activation of AMPA, VDCC and TrkB/BDNF pathway. Altogether, our results elucidate signaling pathways involved in the antidepressant-like effect of guanosine and reinforce the role of these molecular targets in antidepressant responses.

Poster

Chronic glibenclamide treatment prevented stress-induced changes in behavior and dopamine levels in the pre-frontal cortex of mice

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Background: Chronic stress is a risk factor for major depression disorder (MDD). It elicits neurochemical and neuroanatomical changes that negatively impact on brain functioning causing mood dysfunction and cognitive impairment. Dysregulation of the monoaminergic system in MDD has been the principle for antidepressant therapy for several years. However, chronic stress can also promote a dysregulation in the immune system, and an inflammatory profile is frequently observed in patients with MDD. Increased inflammation after chronic stress could also intensify the modification of monoaminergic metabolism and might contribute to the pathophysiology of MDD. Glibenclamide is a hypoglycemic medication able to inhibit ATP-sensitive potassium channels and the activation of NLRP3 inflammasome, a cytosolic protein complex responsible for the maturation and release of the pro-inflammatory cytokines.

Objectives: This study aimed to investigate the potential effect of glibenclamide, in preventing behavioral alterations and changes in the monoaminergic system induced by chronic unpredictable stress (CUS).

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Methods: Female Swiss mice (45 days) were submitted to the CUS. This paradigm maximizes unpredictability and consists of a variety of stressors applied randomly and at varying times of the day, for 21 days. Glibenclamide (5 mg/kg, p.o.) or vehicle (1% DMSO, p.o.) were administered during all the CUS protocol. At the end of CUS protocol, animals were submitted to the open field test to evaluate locomotor activity, to the tail suspension test and forced swim test to evaluate depressive-like behavior, and to the object location test to evaluate short-term memory. Monoamines levels were measured in the pre-frontal cortex and hippocampus by high-performance liquid chromatography (CEUA Nº 5021180116).

Results: Results showed that glibenclamide treatment prevented the depressive-like behavior and short-term memory impairment induced by CUS. In the prefrontal cortex, CUS increased noradrenaline and decreased dopamine. Treatment with glibenclamide alone increased noradrenaline levels, and these levels remained elevated in stressed mice treated with glibenclamide. However, CUS decreased dopamine levels, an effect that was prevented by glibenclamide treatment. No changes were observed in serotonin levels in the prefrontal cortex, or hippocampal levels of monoamines after stress or glibenclamide treatment.

Conclusion: Our results show that glibenclamide treatment successfully prevented behavioral alterations and changes in dopamine levels induced by CUS in the prefrontal cortex. However, more studies need to be performed to confirm the ability of glibenclamide to inhibit NLRP3 complex and consequently decrease neuroinflammation that could be associated with monoaminergic system modulation.

Poster

The Acute Effects Of Low Doses Of Δ9-tetrahidrocanabinol In Anxiety Are Sex And Age-dependent

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Background: Introduction: The Cannabis effect in emotional states is a matter of controversy. In adult males, conventional tested doses of Δ9-tetrahidrocannabinol (THC; 1 – 10 mg/kg), the main compound of Cannabis, are anxiogenic, reduce the animal motivation and impair cognition [1]. In contrast, ultra-low doses of THC have shown to be neuroprotective in males and females, mainly in aged rats [2]. The anxiety disorders are more prevalent in females however, the effect of low doses of THC in anxiety-related behavior in young and aged females is unknown.

Objectives: We aim to evaluate the effect of low doses of THC in anxiety-related behavior in adult and aged female rats.

Methods: Female Wistar rats normally cycling, ovariectomized (OVX) or aged (one year old) received the systemic treatment with THC (0,075, 0.1, 0.3 and 1.0 mg/kg) or vehicle (VEH) 20 minutes before the 5 minutes exposure to the elevated plus-maze (EPM). When appropriate, the vaginal secretion was colected and the groups were allocated according to the hormonal cycle in estrous (ES), pro-estrous (PE) and diestrous (DI). A group of adult male Wistar rats was used as control. The percentage of open-arms entries (%OAE) and time (%OAT) and the number of enclosed-arms entries (EAE) were evaluated and expressed as mean ± E.P.M. Procedures were approved by CEUA#1247.

Results: One-way ANOVA showed significant treatment effect for %OAT [F(4,38)=6,95; P=0,0003] and %OAE =[F(4,38)=6,65; P=0,0004] in PE. The treatment with the 1.0 mg/kg of THC reduced the open-arm exploration, suggesting an anxiogenic-like effect. No changes in EAE was observed. One-way ANOVA showed significant treatment for %OAT [F(4,53)=8,98; P=0,00001], %OAE [F(4,53)=8,40; P=0,00003] and EAE [F(4,53)=2,57; P=0,05] in DI. The treatment with 1.0 mg/kg of THC reduced open-arms exploration and the treatment with 0.075 mg/kg of THC increased the open-arms exploration, suggesting an anxiogenic and anxiolytic-like effect of the highest and lowest doses of THC, respectively. No change in EAE was observed. One-way ANOVA showed significant treatment for %OAT [F(4,44)=6,22; P=0,0005] and EAE [F(4,44)=4,74; P=0,003] in ES. The treatment with 1.0 mg/kg of THC reduced open-arms exploration, suggesting an anxiogenic-like effect. The treatment with 0.3 mg/kg of THC increase the enclosed-arms exploration. No changes in %OAE was observed [F(4,44)=1,70; P=0,17]. One-way ANOVA showed no treatment effect in OVX for %OAT [F(4,30)=1,47; P=0,24], %OAE [F(4,30)=0,49; P=0,75] and EAE [F(4,30)=2,88; P=0,06], in aged rats %OAT [F(4,45)=1,82; P=0,14], %OAE [F(4,45)=1,34; P=0,27] and EAE [F(4,45)=0,48; P=0,75] or in male rats %OAT [F(4,38)=0,93; P=0,46], %OAE [F(4,38)=0,84; P=0,51] and EAE [F(4,38)=0,15; P=0,96], suggesting that the doses of THC tested here do not interfere with anxiety-like state and with locomotion.

Conclusion: The anxiogenic and anxiolytic-like effect of THC depends on the ovarian hormones in cycling females. In aged female rats or in adult males, the tested doses did not change the anxiety-related parameters, reinforcing the hypothesis that low to ultra-low doses of THC are devoid of undesirable effects, such as increases in anxiety state or hypolocomotion.

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Poster

Epigenetic and depression in Parkinson's disease: what is the role for BDNF?

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Introduction: Parkinson's disease (DP) is the second most common neurodegenerative disease and is characterized as a motor neurodegenerative disease. However, among the non-motor symptoms, depression is the most common and the one that most impact the patient's quality of life. Depression in PD is more prevalent in women, its neurobiological basis remains poorly understood and it does not respond effectively to available antidepressant therapies. Agmatine is a substance with known antidepressant effects acting through several mechanisms. Several stimuli such as everyday events, behavioral experiences and the circadian rhythm may induce cellular responses involving epigenetic mechanisms, and it is known that stable epigenetic impressions in specific loci can influence synaptic plasticity and consequently behavior. Diseases such as depression and PD despite the etiology is still not fully understood, it is believed to be a multifactorial diseases, where genetic and environmental factors influence its development. Several studies have already described that in these two pathological conditions epigenetic modifications can contribute to the progression and severity of the disease, as well as to the limitations and difficulties of treatment.

Methods: The animals, female C57BL/6 mice, were allocated according to the following groups: (i) control + vehicle (n=10), (ii) control + agmatine 1 mg/kg (n=10), (iii) MPTP + vehicle (n=8), (iv) MPTP + agmatine 1 mg/kg (n=9). MPTP was administered by intranasal (i.n.) route according to the procedure previously described [1]. The treatment with agmatine 1 mg/kg was made orally during 15 days following i.n. administration of MPTP. To evaluated the role of epigenetic alterations related to Bdnf gene it was performed the immunoprecipitation of methylated DNA (meDIP) using an antibody anti- 5-methylcytosine (anti-5meCyt) and chromatin immunoprecipitation (ChIP) using the following antibodies: mouse anti-H3K9me3 for prefrontal cortex (PFC) samples and rabbit anti-H3Ac3 for hippocampus (HIP) samples. A reverse transcription and real-time quantitative PCR (RT-qPCR) was performed to verify the Bdnf gene expression after MPTP and agmatine treatment.

Results: Statistical analysis showed an increase in DNA methylation in the CpGs islands IV and VI of Bdnf gene in PFC after i.n. MPTP administration. Treatment with agmatine was surprisingly able to prevent such epigenetic modifications related to the transcription of the Bdnf gene. An increase in DNA methylation in the CpGs islands IV and VI of the Bdnf gene in HIP was also observed by the analysis of variance after i.n. administration of MPTP.

Intranasal MPTP administration increased the histone H3 methylation levels in the exons IV and VI of the Bdnf gene and the agmatine treatment was able to reduce this high methylation profile on the exon IV. In contrast, treatment with agmatine has no effect on the increase of methylation on exon VI of Bdnf gene. Statistical analysis demonstrated that i.n. MPTP administration induced a reduction in acetylation of the exons IV and VI of the Bdnf gene in the hippocampus of the animals. Treatment with agmatine prevented the increase in histone H3 acetylation observed following i.n. administration of MPTP on the exons IV and VI.

Discussion: Neurotrophins are implicated in the development, maintenance and function of the central nervous system (CNS). In the CNS, they are involved with synaptic plasticity, proliferation, survival and neuronal differentiation. Thus, changes in the levels of these neurotrophic factors are associated with the development of various neuropsychiatric disorders, such as depression and PD. Epigenetic changes have already been associated with the pathogenesis of depression and PD, and have served as a basis for explaining the complications and refractoriness of treatment that may arise in both diseases. The analysis of variance performed in the experiments showed that both PFC and HIP of mice after i.n. MPTP administration presented an increase in the DNA methylation levels in the CpGs (exons) islands IV and VI, indicating a repression in the transcription of the Bdnf gene in these animals, which can correlate with a reduced level of this neurotrophic factor and consequently damages in the neuronal functions, which can corroborate the emotional deficits associated with PD. Of high importance, the treatment with agmatine (1 mg/kg) was able to avoid hypermethylation of the exons IV and VI of the Bdnf gene, resulting in a lower repression of transcription of this protein, consequently, more balanced levels of BDNF, which may be responsible for its potential in improving the emotional deficits. Our results indicate that i.n. MPTP administration is associated with an increase in histone H3 (H3K9me3) methylation in PFC and a reduction in

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histone H3 (H3Ac3) acetylation in HIP in the exons IV and VI of the BDNF gene, correlating with the silencing and activation of transcript of BDNF, respectively, which may explain the induction of anhedonic-like and depressive-like behaviors. Treatment with agmatine (1.0 mg/kg) reduced the exon IV methylation of the Bdnf gene on histone H3 in PFC and prevented the reduction of histone H3 acetylation in the exons IV and VI of the Bdnf gene in the HIP of the animals.

Conclusion: The results presented reinforce the potential of the animal model of PD induced by i.n. administration of MPTP in the study of the emotional symptoms associated to PD, indicating novel mechanisms that may be involved in the pathogenesis of these symptoms, such as the reduction in the immunocontent of neurotrophins and the epigenetic alterations associated to the Bdnf gene. Furthermore, it was demonstrated the antidepressant potential of agmatine to control of emotional impairments and in the modulation of neurotrophins, and it was demonstrated for the first time the potential of this substance in the management of the epigenetic alterations associated with this animal model of PD.

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Poster

Uliginosin B inhibits ATP and ADP hydrolysis on striatal synaptosomes of rats

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Background: Studies have shown that uliginosin B (ULI), a dimeric phloroglucinol isolated from Hypericum polyanthemum [1], a vegetal specie native to South Brazil, has antidepressant-like effect in rodents, which seem to be at least partially due to the inhibition of synaptosomal uptake of dopamine in the striatum [1] [2]. In addition, ULI (10 mg/kg, p.o) increased Na+K+-ATPase activity in cerebral cortex of mice [3]. Stolz et al. [2] demonstrated that the treatment of mice with ULI (15 mg/kg, i.p) induces antinociception and increases AMP and ATP hydrolysis in spinal cord and cerebral cortex synaptosomes, respectively.

Objectives: In this study, we aimed to evaluate the effect of ULI on the hydrolysis of ATP and ADP in striatal synaptosomes.

Methods: Synaptosomes were isolated from striatum of male Wistar rats and the hydrolysis of ATP, ADP and AMP was performed according to Silva et al. and Nagy et al. [4] [5]. The synaptosomal preparation was incubated with ULI at 0.1 μM, 1 μM, 10 μM and 100 μM.

Results: ULI 0.1 μM, 1 μM, 10 μM and 100 μM decreased by 14%, 8.33%, 21% and 70 % the hydrolysis of ATP, respectively. The best-fit value of IC50 estimated by non-linear regression was 127 μM. The hydrolysis of ADP decreased by 70% at ULI 100 μM only. The hydrolysis of AMP was not affected.

Conclusion: The effect of ULI on the rat striatal synaptosome evaluated in vitro indicates that ULI impairs the activity of E-NTPDases in the rat striatum, which differs from results obtained by Stein et al. [3] and Stolz et al. [2] in spinal cord and cerebral cortex of mice trough ex-vivo experiments. Thus, the effects previously observed on ATP and AMP hydrolysis after systemic administration of ULI to mice may be due ULI metabolites.

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Poster

The differential contribution of protein kinase C and PKMζ located in PL cortex in fear memory reconsolidation and persistence

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Background: The reconsolidation time-window lasts 6 hours[1]. However, the systemic inhibition of protein kinase C (PKC) 6 or 9 h after memory reactivation impaired its persistence[2]. Persistent signaling of atypical isoform of protein kinase C (PKC), Mzeta kinase (PKMζ) maintain long-term synaptic potentiation and long-term memory[4].The prelimbic cortex (PL) activity underlies fear memory reconsolidation[3] and persistence, however, the role of PKC and PKMζ in these processes is undetermined.

Objectives: We aimed to investigate the role of PKC and PKMζ located in PL in memory reactivation-induced reconsolidation and persistence.

Methods: Male Wistar rats with bilateral cannulas aimed at the PL underwent contextual fear conditioning

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thatconsisted of familiarization to the Context (day 1), fear conditioning (3 footshock of 0.7mA/3s; day 2), reactivation (Context exposure for 3 min; day 3), and Context re-exposures to estimate the drug effects 1, 7 or 21 days after memory reactivation (T1, T2 and T3, respectively). Independent groups received vehicle (VEH) or the PKC inhibitor cheleritrin (CHE; 1 or 3 nmol/0,2μL/side) 0, 1, 6, 9, 12 or 18 h after memory reactivation. The zeta inhibitory peptide (ZIP; 10 nmol/0,2 μL/side) or the scrambled-ZIP (scr-ZIP; 10 nmol/0,2 μL/side) were infused into PL 0, 1 or 6 h after memory reactivation. A control group had the memory retrieval omitted, or its reactivation disturbed by the i.p. administration of nimodipine 16 mg/kg, and after 6 h they received VEH or CHE 3 nmol. Freezing behavior was assessed as index of fear memory. Data was analyzed using repeated measures ANOVA followed by Newman-Keuls test ($P \leq 0.05$). CEUA 1011.

Results: The infusion of CHE (1 nmol) into PL immediately after memory reactivation significantly reduced the freezing time in T1 and T2 [$F(4,54)=14.386$; $p=0.00001$], indicating a role for PKC in memory reconsolidation.. VEH-treated animals presented similar percentage of freezing during reactivation, T1 and T2. The groups treated with CHE 1 or 3 nmol intra-PL 6, 9 or 12 h after memory reactivation presented less freezing behavior than controls only during T2 [$F(4,56)=13.712$; $p=0.00001$], suggesting a PKC role in memory persistence. When memory retrieval or its reactivation were omitted, the infusion of CHE 6 h later did not change the freezing expression during T1 and T2. The selective inhibition of PKMζ 1 or 6 h after memory reactivation, reduced the freezing behavior only in T2 and T3 [$F(3,36)=15,104$; $p=0,00001$]. The infusion of ZIP into PL immediately after memory reactivation, did not change the freezing behavior, suggesting a selective role of PKMζ in the reactivation-induced persistence of fear memory.

Conclusion: The findings suggest that PKC activity in PL is necessary for both, reconsolidation and persistence, while PKMζ activity is necessary only for persistence of reactivated fear memory. Altogether, the present findings suggest that different mechanisms in PL cortex underly the reconsolidation and persistence of reactivated fear memory.

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Poster

Protective Effect of Probucol after Manganese-induced Mitochondrial Neurotoxicity in SH-SY5Y cell line

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Background: Introduction: Manganese (Mn) is an essential element required for several biological systems, however, in excess, it could be neurotoxic and lead to a parkinsonian-like syndrome, known as Manganism. The molecular mechanisms of that involves oxidative stress and mitochondrial dysfunction.

Objectives: Objective: This study evaluated the neuroprotective effect of probucol, a lipid-lowering agent with anti-inflammatory and antioxidant properties, on cell viability and mitochondrial oxidative stress in neuroblastoma cell line (SH-SY5Y) exposed to Mn.

Methods: Methods: Cells were incubated with crescent concentrations (0,001 to 5 mM) of Mn and (0,001 to 3 mM) of Probucol for 1, 3, 6 and 24h and association of 0,1 mM Mn + 0,001 mM probucol for 24h to verify the toxic doses and measure the cell viability and mitochondrial complex I activity.

Results: Results: It was observed that prolonged exposure of Mn (24h) promote a decrease on SH-SY5Y cell viability in concentrations of 0,1 mM and over, but not at shorter exposure. Nevertheless, probucol was able to prevent the decrease on cell viability and mitochondrial dysfunction induced by Mn.

Conclusion: Conclusion: These preliminary data suggest that probucol might be a useful strategy to prevent mitochondrial dysfunction-derived oxidative stress in neurodegenerative conditions that involves persistent exposure of Mn.

Poster

The Antidepressant Effect Of Ketamine On The Forced Swim Test In Swiss Mice: A Systematic Review And Meta-Analysis

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Introduction: The Porsolt forced swim test (FST) is one of the most commonly used tests to evaluate the antidepressant-like effect of drugs. However, in recent published studies no differences were found between monoaminergic antidepressants compared to the control group in Swiss strain in previous experiments in our laboratory [1], suggesting resistance to this type of treatment. Our aim is to evaluate the antidepressant-like effect of ketamine, a NMDAr antagonist drug, in FST, through a systematic review and meta-analysis, before to animal experiments.

Methods: The systematic review was performed according to the criteria of the SYRCLE platform for experiments with laboratory animals. The database used was MEDLINE/PubMed. The inclusion criteria were: (1) mice, (2) treated with ketamine, (3) tested in FST. The exclusion criteria were: (I) no Swiss strain, (II) female, (III) no adult, (IV) other treatments, (V) reviews and (VI) co-treatment. For the selected articles, the following items were extracted: author, age, weight, cycle, number of animals in the group, treatment period, dose, immobility in the ketamine group and control, test used and significance. The meta-analysis was then performed to evaluate the data collected using Hedges' g effect size. Heterogeneity was analysed using I2 parameter. Meta-regression and subgroup sensitivity analysis were also used to identify possible sources of heterogeneity.

Results: Of the total 157 references, only 10 articles were selected for the review. The % of immobility reduction had great variation in the articles. The total effect size was 0,76 ± 1,19. The meta-regression showed that ketamine had a significant antidepressant-like effect, especially in relation to the dose used, with antidepressant-like effect correlated with high doses (β = 0,63, $p<0,001$), the exception was the dose of 100 mg/kg, with high immobility compared to the control. The level of heterogeneity was high, and the subgroup analysis showed that the effect size varied considerably depending on the dose and authorship of the work. Risk of bias assessed with funnel plot, Trim and Fill and Egger regression of the results was low.

Conclusion: The overall effect size of ketamine was positive, but no significant. However the high doses of ketamine showed significant effect compared to control and low doses of ketamine, suggesting that the effect is consistent only with high doses.

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Conflicts of Interest

The authors declare that there is no conflict of interest in the above work

Poster

Effects of pramipexole on ultrasonic vocalization and depressive-like behavior in animal model of Parkinson's disease.

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Introduction

Parkinson's disease (PD) is clinically characterized by the occurrence of motor symptoms, such bradykinesia, tremor at rest and muscular rigidity, wich are associated the consequence of the death of dopaminergic neurons located in the substantia nigra pars compact (SNpc) and dopamine striatal (DA) depletion. However there is also the occurrence of non-motor symptoms such as mood disorders as depression and anxiety, REM sleep behavior disorder, among others [1].

Depression is the main non-motor symptom evidenced in PD, about 40% to 50% of PD patients develop, making it clear that there is a considerably high risk of PD depression, directly affecting patients' quality of life regardless motor symptoms [2]. Antiparkinsonian drugs are often effective in treating motor symptoms, but they do not demonstrate improvement in depression associated with PD, making the treatment of these patients another challenge [3].

Several clinical studies have shown that pramipexole (PPX) a full agonist at dopaminergic receptors of the D2 subfamily, is effective in the management of depression associated to PD. It's effectiveness maybe due to the action on D2 and D3 receptors located in the nucleus accumbens [4].

Some studies have indicated that PPX is also effective at the beginning of depression treatment and patients who are refractory to other typical antidepressants respond with improvement of depressive symptoms within four weeks of the initiation of treatment [5].

Thus, the main objective of this study is to evaluate the effect of pramipexole on ultrasonic vocalization and depressive-like behavior in 6-OHDA-lesioned rats, animal model of PD.

Methods

Male Wistar rats (280–320g), were used.All tests and procedures were conducted in accordance with the Ethics Committee for Animal Research of the Federal University of Paraná (CEUA- Protocol #1206). Experiment 1: the sucrose preference test and ultrasonic vocalization test were performed 7 days

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before the stereotactic surgery to evaluate the basal preference of rats, and the emission of spontaneous calls respectively. After surgery animals were evaluated weekly (7,14,21 and 28 days) in sucrose preference, and in vocalization ultrasonic test on 14 and 28 days after starting the treatment. The 6-hydroxydopamine (6-OHDA) rats were treated with vehicle, pramipexole (1.0 mg/kg) or imipramine (20 mg/kg). The treatment was started 1 hour after the surgery, and once daily for 28 days. Experiment 2: the same rats of experiment 1 were tested in the forced swimming test at end of the all experiments. The behaviors evaluated were the behavior of immobility, climbing, and swimming for 5 minutes. Experiment 3: immunohistochemical analysis of substantia nigra pars compact was performed to evaluate the lesion induced by the 6-OHDA. Experiment 4: neurochemical analysis of striatum, to quantify serotonin and dopamine and its metabolites.

Results

In the sucrose preference test, it was observed that, after the 6-OHDA lesion, there was a reduction in sucrose consumption in the vehicle group ($p = 0.049$), indicating a depressive-like behavior. Similarly, the lesioned group treated with pramipexole showed a reversal of this condition after the 14th day of treatment. In the forced swimming test it was observed that the pramipexole treated groups had an increase in swimming time compared to the untreated controls ($p < 0.0001$), suggesting a probable antidepressant effect and possibly an interaction with the serotonergic system. In the ultrasonic vocalization test, animals treated with pramipexole (or PPX) showed an increase in total vocalization time and in the quantity and subtypes of vocalizations emitted compared to vehicle-treated 6-OHDA group ($p < 0.0001$). The immunohistochemical analysis showed that the treatment with pramipexole was not able to reverse the death of neurons on SNpc indicating 55% ($p=0.0024$) and 66% ($p=0.0060$) of death of these neurons for the groups treated with vehicle and pramipexole respectively. In the neurochemical analysis the data indicated that the pramipexole was able to increase the amount of serotonin($p<0.05$) and dopamine ($p<0.05$) in the striatum of these animals.

Conclusion

Our data indicate that pramipexole was not capable to protect dopaminergic neurons in the SNpc from 6-OHDA toxicity. However, pramipexole was able to reverse the anhedonic state in these animals evidenced in the sucrose preference, forced swimming test and ultrasonic vocalization. In addition, the data of neurochemical analysis indicated the interaction between the monoaminergic systems, evidencing the importance of these interactions for the understanding of important mechanism of mood disorders.

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Poster

Could the "biased" 5-HT1A receptor agonists F15599 and F13714 change the pattern separation performance and hippocampal plasticity in aged rats?

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Background: Introduction: Pattern separation, or the formation of distinct representations out of similar inputs, is an important hippocampal process implicated in memory formation [1]. During the natural aging reduction in gray matter, especially in the hippocampus, decreases pattern separation ability [2]. Due the distribution of serotonin (5-hydroxytryptamine, 5-HT) and its receptors in the hippocampus, especially in the dentate gyrus (DG), compound which modulates its expression in this strategic areas has been investigate as a pro-cognitive drug [3]. Previous study demonstrated that acute treatment with the new 5-HT1A "biased" agonist, F15599, which preferentially activates postsynaptic heteroreceptors, improved naïve young rats performance in the object pattern separation (OPS) task. In contrast, F13714, which preferentially activates presynaptic autoreceptors, impaired performance of young rats in this task [4].

Objectives: Objective: Herein, we investigated the effects of single and repeated treatment with F13714 or F15599 on OPS performance of aged rats. We also investigated the hippocampal expression of neuroplasticity markers.

Methods: Methods: Aged male Wistar rats 20 months old (CEUA nº 2675220317) received i.p. single or repeated (14 days) injections of F15599 (single injection: 0.08 mg/kg and repeated injection: 0.32 mg/kg), F13714 (single injection: 0.0025 mg/kg and

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repeated injection: 0.02 mg/kg) or vehicle (saline). OPS performance was measured at day 1 and 15. Core body temperature was measured daily, 30 min after each drug administration. At the end of the behavioral tests the animals were sacrificed and their brains were removed for immunoassay analysis. Behavioral data was analyses by one-way analysis of variance (ANOVA) followed by Tukey-Kramer's multiple-range test. Generalized linear model with a Poisson or Gamma distribution was employed for immunoassay data.

Results: Results: F15599 resulted in enhancement of OPS performance compared to vehicle, and this was maintained until day 15 (F2,33=5-5 - 8.9, p =0.009 - 0.001). F15599 also decreased body temperature from the first day of treatment compared to rats which received vehicle (F2,33=2.9 - 13.9, p = 0.1 - <0.0001). F13714 resulted in no effect on OPS performance, however F13714 caused a drop in core body temperature at day 7 onwards ($p < 0.05$). Both compounds increased the number of doublecortin (DCX)-positive neurons ($x2 = 11.92$, $p = 0.002$), but only F15599 increased the hippocampal expression of Post synaptic density protein 95 (PSD95) ($x2 = 237.5$, $p < 0.05$) and Brain-derived Neurotrophic Factor (BDNF) ($x2 = 400.4$, $p > 0.05$).

Conclusion: Conclusion: These data suggest that F15599, which preferentially activates postsynaptic heteroreceptors, might be a useful therapeutic strategy to improve the OPS performance in aged rats. Financial support: Capes, Universidade Estadual de Maringá, Maastricht University.

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Poster

Could the "biased" 5-HT1A receptor agonists F15599 and F13714 change the pattern separation performance and hippocampal plasticity in aged rats?

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Objectives: Objective: Herein, we investigated the effects of single and repeated treatment with F13714 or F15599 on OPS performance of aged rats. We also investigated the hippocampal expression of neuroplasticity markers.

Methods: Methods: Aged male Wistar rats (20 – 24 months) received i.p. single or repeated (14 days) injections of F15599 (single injection: 0.08 mg/kg and repeated injection: 0.32 mg/kg), F13714 (single injection: 0.0025 mg/kg and repeated injection: 0.02 mg/kg) or vehicle (saline). OPS performance was measured at day 1 and 15. Core body temperature was measured daily, 30 min after each drug administration. At the end of the behavioral tests the animals were sacrificed and their brains were removed for immunoassay analysis. Behavioral data was analyses by one-way analysis of variance (ANOVA) followed by Tukey-Kramer's multiple-range test. Generalized linear model with a Poisson or Gamma distribution was employed for immunoassay data.

Results: Results: F15599 resulted in enhancement of OPS performance compared to vehicle, and this was maintained until day 15 (F2,33=5-5 - 8.9, p =0.009 - 0.001). F15599 also decreased body temperature from the first day of treatment compared to rats which received vehicle (F2,33=2.9 - 13.9, p = 0.1 - <0.0001). F13714 resulted in no effect on OPS performance, however F13714 caused a drop in core body temperature at day 7 onwards ($p < 0.05$). Both compounds increased the number of doublecortin (DCX)-positive neurons ($x2 = 11.92$, $p = 0.002$), but only F15599 increased the hippocampal expression of Post synaptic density protein 95 (PSD95) ($x2 = 237.5$,

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p <0.05) and Brain-derived Neurotrophic Factor (BDNF) (x22 = 400.4, p > 0.05).

Conclusion: Conclusion: These data suggest that F15599, which preferentially activates postsynaptic heteroreceptors, might be a useful therapeutic strategy to improve the OPS performance in aged rats.

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Poster

Mynocicline Pre-Treatment Did Not Prevent The Behavioral Changes Induced By High-Refined Carbohydrate Diet Consumption In Mice

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Background: The excessive ingestion of foods rich in fats and carbohydrates are associated with adipose tissue expansion leading to development of obesity [1]. The main characteristic of obesity is a chronic-low grade inflammatory response, which is not limited to periphery but also could be associated to neuroinflammatory process [2]. It´s a result of the activation of glial cells, leading to profound molecular and morphological changes that would alter the behavior, facilitating the development of several disorders, including depression and anxiety [3]. Minocycline, a second-generation antibiotic, has been proposed to be capable to reduce the inflammation and microglial-induced inflammatory response. Moreover, several data propose this drug as a new candidate to antidepressant drug [4].

Objectives: The aim of this study was evaluate if the minocycline treatment was able to reverse the anxiety and depressive-associated behaviors induced by chronic consumption of high-refined carbohydrate diet (HC) in mice.

Methods: Male Balb-C mice received standard diet or HC diet for 12 weeks. On 11th week, the animals received daily i.p injections of minocycline for 7 days (50mg/kg). One day after the last injection, mice were subjected to the Tail Suspension Test (TST), Novelty Suppressed Feeding (NSF) or Marble Burying (MB) Test (CEUA: 65/2017).

Results: As already described the HC diet induced an anxiogenic-like effect in the NSF test (diet effect F(1.39) = 4.17 p=0.04, drug effect F(1.39) = 0.32 p>0.05, drugXdiet effect F(1.39) =0.52 p>0.05 Two-Way ANOVA) and a compulsive-like behavior in the MB Test (diet effect F(1.23) = 5.60 p=0.02, drug effect F(1.23) = 0.06 p>0.05, drugXdiet effect F(1.23) =0.001 p>0.05 Two-Way ANOVA). No difference in immobility time in the TST was observed (diet effect F(1.40) = 0.09 p>0.05, drug effect F(1.40) = 2.15 p>0.05, drugXdiet effect F(1.40) =1.87 p>0.05 Two-Way ANOVA). The minocycline was not able to reverse such behavioral changes.

Conclusion: Our findings confirm previous data from our group, indicating that chronic HCD consumption promotes anxiety and compulsive behaviors. However, minocycline treatment was not able to reverse these alterations. These results suggest that microglial activation may not be responsible for the behavioral changes induced by HC diet consumption in mice. FINANCIAL SUPPORT: CNPq / CAPES.

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Poster

The phosphodiesterase 4 inhibitor roflumilast potentiates the fear memory extinction persistence: a putative involvement of the infralimbic cortex

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Background: The selective PDE-4 inhibitor roflumilast (ROF) enhance the intracellular signaling cAMP/PKA/CREB pathway[1], which is critical for memory consolidation and persistence[2], however, the role in fear memory extinction is contradictory[2,3]. To potentiate the memory extinction persistence is important because exposure-based therapy used in the treatment of posttraumatic stress disorder is based in extinction process.

Objectives: To evaluate the systemic effects of ROF in the acquisition, early and late consolidation phases of fear memory extinction, as well as the ROF effects into

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the infralimbic (IL) cortex (necessary for extinction consolidation).

Methods: Male Wistar rats were submitted to the fear conditioning protocol that consisted of familiarization (3 min), fear conditioning (3 footshocks of 0.7 mA or 0.8 mA for 3 s, inter-shock interval 30 s), fear extinction session (ES; 20 min) and extinction recall 1 (ER1; 3 min). These sessions were conducted 24 h apart. Ten days later, the animals were re-exposed to the second extinction recall test (ER2). ROF (0.01, 0.03 or 0.1 mg/kg) or vehicle (VEH) were given i.p. 20 min before or 5 min, 3 and 6 h after ES. An additional group received vehicle or ROF (9 ng/0.2 µL) into the IL cortex. Freezing behavior was analyzed and expressed as mean ± S.E.M. Elevated plus maze (EPM) and light-dark transition (LDT) tests were performed to evaluate the anxiety and exploratory behaviors. The same doses of ROF was administered 20 min prior these tests. All experimental protocols were approved by CEUA#1161.

Results: Repeated measures ANOVA showed an interaction between treatment and time-bin factors during the extinction session for freezing time [$F(12,176)=2.91$; $P<0.05$]. ROF 0.03 mg/kg administered 20 min before ES reduced the freezing behavior during the first 4-min block extinction. No effect was observed during ER1 or ER2, suggesting a within session effect. When ROF was administered during the early consolidation phase, no effects were observed in ER1 or ER2 [$F(3,40)=3.65$; $P > 0.05$]. Repeated measures ANOVA showed significant treatment effects for freezing time during ER1 and ER2 [$F(3,32)=3,32$; $P < 0.05$]. ROF 0.03 administered 3 h after ES specifically reduced the freezing behavior during ER2, suggesting a potentiation of extinction memory persistence. No effect was observed when ROF was administered 6 h after ES [$F(3,40)=3.65$; $P > 0.05$]. Repeated measures ANOVA showed a significant interaction between drug treatment and context re-exposure for freezing time during ER1 and ER2 [$F(1,13)=4.60$; $P < 0.05$]. ROF injected into the IL cortex 3 h after ES reduced the freezing behavior compared to control during ER2, reinforcing the previous data suggesting that ROF potentiates the extinction memory persistence. Importantly, the doses tested herein did not change the anxiety- or exploratory-like behavior in EPM or LDT.

Conclusion: Our findings showed that inhibiting the PDE-4 during the late consolidation improved the extinction recall only eleven days after treatment, suggesting a potentiation of extinction memory persistence. Acknowledgments: CAPES and NUFFIC by financial support.

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Poster

Agomelatine's effect on circadian locomotor rhythm alteration and depressive-like behavior in a 6-OHDA rat model of Parkinson's disease

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Background: Parkinson's disease (PD) is a neurodegenerative disorder mainly considered as a motor disorder, PD is characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and consequent reduction of dopamine in striatum. However, the neurodegeneration also causes a set of non-motor symptoms frequently reported by PD patients, such as sleep-circadian rhythm alterations and depression. It is known that toxin-based animal models of PD can induce circadian rhythms alterations and depressive-like behavior. We hypothesized that agomelatine (melatonin MT1/MT2 receptor agonist and serotonin 5-HT2C receptor antagonist), an antidepressant with potential to resynchronize disturbed rhythms, could prevent rhythm alterations and depressive-like behavior in the 6-hydroxydopamine (6-OHDA) model.

Objectives: The aim of the present study was to analyze the effects of agomelatine treatment over possible alterations in the circadian cycle of locomotor activity and the loss of dopaminergic neurons in the SNpc in the 6-OHDA Parkinson's disease rat model. Also, evaluate the possible antidepressant-like effect of agomelatine treatment in parkinsonian rats.

Methods: Male Wistar rats, 75 days old (n=78) were used (Universidade Federal do Paraná Ethics Committee protocol no. 906). Experiment 1: the animals were maintained in individual cages and the locomotor activity was continuously monitored for 7 days before the stereotaxic surgery as baseline, and for 21 days after the 6-OHDA lesion. Experiment 2: the same procedures of experiment 1 were performed, however, the animals were treated with vehicle or agomelatine (50 mg/kg) once daily for 21 days after surgery. Experiment 3: the rats underwent 6-OHDA lesion and after surgery were treated with vehicle or agomelatine (50 mg/kg) once daily for 21 days. The animals were tested weekly for sucrose preference until day 21.

Results: The two-way ANOVAs and Newman-Keuls post-hoc tests indicated that: a) in experiment 1, animals significantly showed on week 1 after lesion a more diurnal activity [$F(3, 60) = 2.96$, $p = 0.04$] ($p<0.01$), and an impairment in rhythm robustness [$F(3, 60) = 5.54$, $p = 0.002$] ($p<0.05$) and acrophase [$F(3, 60) = 4.20$, $p = 0.01$] ($p<0.001$), also, a decrease

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in rhythm amplitude in week 3 after lesion [F(1, 20) = 9.91, p = 0.005] (p<0.05), which most likely happened due to the loss of 60% of dopamine neurons in the SNpc (Student's t-test, p<0.0001); b) in experiment 2, the 6-OHDA infusion induced a reduction of 55% of SNpc dopaminergic neurons in the 6-OHDA+veh group (p<0.001). The 6-OHDA+ago group had a more discrete neuron loss (40%, p<0.01), however, it was not a significant protection. The analysis indicates that the agomelatine treatment contributed significantly [F(1, 15) = 6.28, p = 0.02] to the decrease of rhythm robustness (p<0.05) and amplitude [F(1, 15) = 4.52, p = 0.05] (p<0.01) in rats treated with the drug; c) in experiment 3, the reduction of dopaminergic neurons in SNpc caused by 6-OHDA lesion led to a significant decrease in sucrose preference [F(1, 39) = 7.07, p = 0.01], however, agomelatine did not induce changes in the sucrose preference.

Conclusion: Our data indicate that agomelatine was not capable of protect dopaminergic neurons in the SNpc from 6-OHDA toxicity; moreover, agomelatine significantly decreased the rhythm robustness and was not able to induce significant changes on other circadian parameters and in sucrose preference impairment in SNpc lesioned rats.

Poster

Caffeine plus exercise improves cognitive and emotional impairments and synaptic plasticity in an animal model of adhd

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Background: The attention deficit/hyperactivity disorder (ADHD) affects 5% of children and adolescents worldwide, and is known by its cardinal symptoms: hyperactivity, inattention and impulsivity. Remarkably, ADHD subjects are more susceptible to develop psychiatric disorders such as depression. Previous non-clinical and clinical studies have demonstrated the benefits of caffeine treatment and physical exercise as independent approaches. Herein we addressed the effects of voluntary exercise plus caffeine intake in behavioral and neurochemical alterations in spontaneously hypertensive rats (SHR), an animal model of ADHD.

Objectives: The aim of this study was to evaluate the effects of chronic caffeine consumption and physical exercise in behavioral and neurochemical alterations in an animal model of ADHD.

Methods: Male SHR (28 days-old) were exposed to volunteer exercise in running wheels and caffeine consumption (0,3 mg/L) during 6 weeks. After that they were submitted to the object recognition (OR) and forced swimming tasks to address short-term recognition memory and depressive-like behaviors. At the end of the behavioral analysis, the levels of different synaptic proteins (SNAP-25, synaptophysin and syntaxin) were measured in the prefrontal cortex and hippocampus by western blotting. This study was approved by Ethic Committee for Animal Use from UFSC (CEUA-UFSC 2635190418).

Results: Caffeine and physical exercise alone or their association improved the object recognition ability and depressive-like behaviors of SHR. The association of caffeine and physical exercise increasedSNAP-25 levels in the prefrontal cortex and hippocampus, and the levels of syntaxyn and synaptophysin only in the prefrontal cortex.

Conclusion: This study provides the first evidence that the association of chronic consumption of caffeine plus physical exercise improves cognitive impairments and depressive-like behaviors in an animal model of ADHD. These benefits were accompanied by the increased expression of synaptic proteins in the PFC and hippocampus.

Financial Support: CAPES, CNPq, FAPESC.

Poster

Exercise did not change the corticostriatal metaplasticity in L-DOPA-induced dyskinesia in 6-hydroxydopamine-lesioned mice

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Background: Physical exercise has been shown in animal models, as well as, in patients a potent antidyskinetic agent. Objectives: The aim of this study was to evaluate the effects of treadmill exercise on striatal metaplasticity in dyskinetic mice induced by L-DOPA.

Methods: C57BL/6 male mice (8-12 weeks, ± 20 g) were treated with 6-hydroxydopamine (6-OHDA, 3 µg in 1 µL of 0.02% ascorbic acid diluted in 0.9% NaCl), in two different regions of the right mid-striatum (2 x 2 µL, 0.5 µL/min) to mimic a hemiparkinsonism. After 4 weeks, they were challenged with R(-)-apomorphine (0.6 mg/kg, subcutaneous), to confirm the lesion. During 30 days the sedentary and exercised groups received a daily intraperitoneal (i.p.) injection with L-DOPA (25 mg/kg) plus benserazide (12.5 mg/kg). At the same time the exercised group started a run in treadmill during 30 minutes per day during 4 weeks

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and both groups were weekly evaluated in dyskinesia score. The animals were then sacrificed and their brain removed to prepare striatal coronal slices (400 µm) used to measure corticostriatal transmission and synaptic plasticity assessed (WinLTP 2.20b Reanalyzes® software) 30 min after applying a high frequency stimulation protocol (HFS: 100 Hz, 3 times, every 20 seconds). We compared 6-OHDA-lesioned striatal slices in saline group, sedentary and exercised dyskinetic animals (n=6-10 independent preparations per group). All procedure used in this study were previously approved by authority responsible in animal welfare (ORBEA), protocol 138-2016/1507201.

Results: The exercised group showed a decrease in dyskinesias score in comparison with sedentary group. The slices from mice with L-DOPA-induced dyskinesia displayed a shift in striatal plasticity to long-term potentiation (LTP) 6-OHDA side in comparison to the 6-OHDA slices from animals only treated with saline. Notably, the chronic exercise did not change dyskinetic striatal plasticity.

Conclusion: In this protocol, treadmill exercise had an antiydiskinetic effect. These findings demonstrate that animals with L-DOPA-induced dyskinesia display alterations in striatal metaplasticity and exercise did not change this scenario. Dopamine treatment in-vitro (50µM) in slices of naïve animals shows the same pattern in metaplasticity.

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Poster

Behavioural evaluation and sexual differences after maternal separation in Wistar rats

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Background: The perinatal period is critical for the development of the central nervous system. The brains of fetuses or newborns are particularly sensitive to remodelling induced by environmental factors and adverse experiences [1]. Animal models are useful tools that help to understand the factors impacting the brain in early life [2]. Maternal deprivation (MD) in critical periods, for example, and may cause neurochemical and behavioural changes in the offspring of rats persisting into adulthood [3].

Objectives: The objective of this work was to delineate the behavioural profile of adult rats which undergo the MD when the connections from hippocampus to the cortex are on development [4].

Methods: On the 9th postnatal day (PND) the dams (Female, adult Wistar rats, ethical committee approval CEUA/UFSC-PP8080/17) were removed from their litters, and the offspring were kept in the nest on a heating pad (34º±2). Twenty-four hours later, progenitors were returned to their litter until weaning (at PND 21) [5]. Between 120-130 PND, the offspring of Wistar rats (males and females, n=8/sex) was evaluated in a battery of tests consisting of the Forced Swim Test (FST) followed by the Novelty Suppressed Feeding (NSF) and then by sucrose preference (SP) separated seven days apart.

Results: Males submitted to MD were longer time immobile in the FST (142.74 s ± 25.7) as compared to control group (75.51 s ± 14.05) (t-test p=0.03). Females submitted to MD were shorter time immobile in the FST (47.05 ± 8.74) as compared to control group (99.18 ± 17, 20) (t-test p=0.03). The immobility time of males in the FST was significantly higher than females when they all undergone MD (t-test p=0.01) but not in the control conditions (t-test p=0.23). The outcomes of the NSF and SP were similar between males or females from MD or control groups.

Conclusion: The results indicate that the MD had different consequences for male and female rats in adulthood. The coping with stress seemed more affected by MD than other behavioural domains in a sexually dimorphic fashion.

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Poster

Fasting increase the preference for palatable food in Drosophila melanogaster

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Background: Drosophila melanogaster may be an organism suitable to replace vertebrates in

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neuroscience research [1][2]. Drosophilidae may express preferences for palatable foods [3].

Objectives: In this study, we investigated the capacity of fasting to increase the preference of D. melanogaster for palatable food (banana).

Methods: Forty adult D. melanogaster wild flies (males, 20/group) were anesthetized in ice (1-3 min) to sexing, transferred to glass containers with corn medium and then assigned to fasted or fed groups. Fasting flies stayed in a falcon tube containing a paper soaked water for 16 hours in groups to avoid social isolation. For behavioural testing, flies were transferred individually using a entomological vacuum cleaner to a plus maze with four arms, three containing agar and one containing banana. The positions of the arms were randomly selected. All the tests were videotaped for 900s under dark conditions to avoid positive-phototaxis influencing the behavior. Ethological analysis was performed with the aid of EthoWatcher®. We analyzed the time that flies spent in the arms and in the center of the maze. All data is expressed as mean±SEM.

Results: Fed flies spent more time in the center of the maze (591.8±32.03s) than fasted flies (385,5±44,40s), T-test, p=0.00073. Control group flies had a lower presence in the banana arm (180.15±35.89) when compared to the fasting group (408.75±52.29), the difference was significant (T-test, p=0.00116). Flies of the fed group explored all arms containing agar slightly longer (Agar 1=19.85±4.24; Agar 2=25.9±5.46; Agar 3=45.25±13.00) than fasted group (Agar 1=17.75±4.90; Agar 2=19.5±9.77; Agar 3=37.2±9.59), (T-test, Agar 1 p=0.75394; Agar 2=0.58062; Agar 3=0.63024).

Conclusion: In general, the flies had a greater presence in the center when compared to the arms, however, when fasting, the presence of the flies in the arm containing banana increased significantly indicating that fasting influenced their permanence in the plus-maze. But, more tests are needed, using females and with a larger sample number.

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Poster

Thalamic Nucleus Reuniens and Memory Updating

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Background: The thalamic nucleus reuniens (NR) is considered a hub for mnemonic processing depending on the hippocampus and the medial prefrontal cortex. Its reciprocal connections with the brain areas abovementioned are well established, however, little is known about its potential contribution to aversive memory updating. Memory updating refers to the inclusion of new information in the beforehand consolidated memory. It makes memories flexible and adaptable to novel information and environments. Based on the above, we hypothesized the activity in the NR could interfere with the destabilization of a contextual fear memory.

Objectives: To investigate whether temporary NR inactivation could affect memory destabilization and, consequently, prevent pharmacologically induced impairments in the reconsolidation process.

Methods: Adult male Wistar rats went through stereotaxic surgery aiming at the NR. Ten days later, they were conditioned to context A with three footshocks. The day after contextual fear conditioning, animals received the vehicle, the GABA-A agonist muscimol (4.0 nmol/0.2 µL) or the proteasome inhibitor clasto-lactacystin beta-lactone (32 ng/0.2 µL) intra-NR 10 min before the context A re-exposure for five min without footshock presentation. The latter session was called reactivation because it had the objective of destabilizing the memory. The muscimol infusion aimed at inhibiting the NR activity while the clasto-lactacystin beta-lactone infusion aimed at preventing the protein degradation necessary for memory destabilization. Animals were also treated immediately after the reactivation session with the adrenergic alpha-2 agonist clonidine (0.3 mg/kg, i.p.) or the protein synthesis inhibitor anisomycin (80 µg/0.2 µL intra-NR) once both agents have been shown to impair the reconsolidation process. The next day, rats were again exposed to the paired context and their freezing levels were quantified (Test A). Twenty-four hours later, animals were also exposed to an unpaired novel context (Test B). CEUA protocol number 9263110516

Results: Both vehicle-clonidine and vehicle-anysomicin groups presented a significant ($p \square 0.05$) reduction in freezing values during Test A when compared with levels from respective controls in the reactivation session, confirming a reconsolidation disruption. This effect was no longer observed in animals pretreated with either muscimol or beta-lactone, indicating that both interventions have prevented the memory destabilization. There were no significant differences among groups during the reactivation session and Test B.

Conclusion: The present results suggest that neither pharmacologically silencing the NR during reactivation nor blocking the local proteasome activity affected the expression of fear memory. However, both interventions were able to prevent fear memory destabilization in the NR. Of note, blocking the destabilization process did not interfere with fear

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memory specificity. Altogether, the NR is a neural substrate for fear memory destabilization and updating.

Poster

A Single Injection of the Organophosphorus Triazophos Induces a Depressive, But Not an Anxious-like Behavior in Rats

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Background: Organophosphorus compounds (OPs) are widely used in agriculture for pest control, especially in developing countries such as Brazil. Some studies have shown that chronic exposure to OP may induce neuropsychiatric disorders such as depression, as well as may increase rates of suicide attempts [1]. Other clinical studies and case series suggest that even acute exposure to OP in various circumstances increases the risk of depression in humans [2]. Similarly, our group observed that a single exposure to a subletal dose of the OP chlorpyrifos induced a depressive-like effect in rats evaluated in the forced swimming test (FST). These animals presented a decrease of acetylcholinesterase (AChE) activity in the hippocampus [3]. An open question is whether other OPs also would induce the same behavioral and biochemical impairment.

Objectives: Therefore, we tested whether a single exposure to sub-lethal doses of triazophos, another, OP, would induce behavioral changes related to anxiety and depression as well as would decrease hippocampal AChE activity.

Methods: Adult male Wistar rats were acutely intoxicated (by intraperitoneal route) with sub-lethal doses of a commercial formulation of TZF (Hostathion 400 BR) at the doses of 7.5, 15, 30 and 45 mg/kg, defined according Singh results [4], or saline (control group) and were evaluated for acute toxicity up to 4 h. Twenty-four hours later, they were tested in the elevated plus-maze (EPM) and in the open field (OF) for assessing anxiety-like behaviors and locomotor activity. Plasma butyrilcholinesterase (BChE) and hippocampal AChE activity from these animals were measured as markers of intoxication. Independent groups of animals were submitted to the FST. All procedures were approved by the Animal Research Ethics Committee of UFES (29/2017).

Results: Triazophos induced signs of acute cholinergic toxicity and reduced plasma BChE and hippocampal AChE activity. All doses of triazophos increased the frequency of immobility, while reduced the frequency of swimming in FST, suggesting a depressive-like effect in these animals. However, acute exposure to triazophos did not change behaviors in the EPM and OP.

Conclusion: This study suggests that a single exposure to triazophos induces a depressive-like behavior without affecting anxiety-like behavior and spontaneuous locomotor activity. Our results also suggest that the depressive-like behavior induced by triazophos is related to the reduction of hippocampal AChE activity.

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Poster

Effect of phosphodiesterase-4 inhibitor roflumilast on the extinction and generalization of contextual conditioned fear memory in streptozotocin-induced diabetic rats

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Background: Clinical and preclinical studies show that diabetes mellitus (DM) impairs spatial learning and memory processes. Moreover, an impairment in the processing of aversive memory has been demonstrated along with a more pronounced anxiety-like response. Several studies indicate that an imbalance between the cyclic nucleotides adenosine monophosphate (cAMP) responsive element binding protein (CREB) and phosphorylated CREB (pCREB) in brain areas involved in the mediation of emotional responses, such as hippocampus and prefrontal cortex, has been involved with the dysregulation of learning/memory processes. Given that phosphodiesterases-4 (PDE4) are enzymes responsible for the breakdown of cAMP into their respective inactive form, the use of the phosphodiesterase type 4 inhibitor (PDE4-i), which increases cAMP and consequently the CREB/pCREB signaling pathway has been pointed out as an important option for the treatment of some cognitive disorders.

Objectives: Thus, the present study aimed to evaluate the effect of the PDE4-i roflumilast on extinction and generalization of fear conditioned memory to the

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context in animals with experimental DM induced by streptozotocin.

Methods: Male Wistar rats received one injection of streptozotocin (60 mg/kg; ip; day 0) to induce diabetes (DBT) while the non-diabetic (nDBT) animals received the citrate buffer. Seven days after induction of DM experimental, DBT animals received PDE4-i roflumilast (i.p.; 0, 0.01, 0.03, 0.1 mg/kg; ip) for 21 days, while nDBT animals received saline vehicle (i.p.) during the same time. At the 25th day after diabetes induction, the animals were submitted to the contextual fear conditioning (CFC) protocol which is composed of: familiarization (context A, 3 min, 25th day), contextual fear conditioning (context A, 3 footshocks of 1mA with 30s of interval before and after each shock, 26th day), extinction training (context A, 20 min, 27th day), extinction test (context A, 3 min, 28th day) and generalization (context B, 3 min, 29th day). As an indicator of fear memory, the freezing time was quantified. All protocols were approved by the Ethics Committee for the Use of Animals of the Biological Sciences Sector of the Federal University of Paraná (#1204).

Results: Partial results indicate a tendency of treatment with PDE4-i roflumilast in facilitating the extinction of aversive memory and decreasing the generalization of the aversive memory in DBT animals.

Conclusion: However, more experiments will be performed to confirm this partial conclusion comparing with data obtained from nDBT and DBT animals treated with vehicle.

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Poster

The antidepressant effect of Rapanea ferruginea and its majoritary compound myrsinoic acid B in diabetic rats is associated with a reduction of the oxidative stress in the prefrontal and hippocampal cortices

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Background: Major depressive disorder (MDD) is one of the most prevalent mental disorders today and affects approximately 322 million people worldwide. MDD is a common comorbidity in patients with diabetes mellitus (DM), and a possible pathophysiological mechanism that correlates the two diseases is the increase in oxidative stress due to hyperglycemia. Rapanea ferruginea Mez. (Primulaceae) is popularly known as “capororoca". Studies indicate that the plant exhibits diverse pharmacological properties which can be attributed to myrsinoic acid A (MAA) and B (MAB). Previous results demonstrated plant effects on the central nervous system, leading us to explore possible psychotropic effects.

Objectives: The objectives of this study were to evaluate the antidepressive properties of the prolonged treatment of hydroalcoholic extract of the bark of R. ferruginea (HEBRF) and the isolated compounds MAA and MAB on behavioral responses related to depression and

Methods: We investigated the action of HEBRF (150 mg/kg, o.g.), MAA (5 mg/kg, o.g.) or MAB (3 mg/kg, o.g.) on the depressive behavior of streptozotocin-induced diabetic rats (STZ, 75 mg/kg, i.p.)(1,2). Animals treated for 28 days after STZ injection were submitted to forced swimming test (FST) and open field test (OFT). The levels of lipid peroxidation (LOOH), reduced levels of reduced glutathione (GSH) and activities of the catalase (CAT) and superoxide dismutase (SOD) enzymes in the HIP and PFC were measured for analysis of the action on oxidative stress parameters. The experimental protocol was approved by the local Ethical Committee (CEUA/UNIVALI 002/17).

Results: In relation to the depressive behavior of STZ-induced diabetic rats submitted to FST, HEBRF and MAA showed no changes in behavior, but MAB reduced immobility time when compared to vehicle-treated diabetic rats, although none of the three treatments prevented the increase in plasma glucose levels or weight loss caused by DM. Treatment with HEBRF, MAA and MAB were able to reduce the increased activity of CAT and SOD due to hyperglycemia and were also able to decrease the levels of LOOH in the HIP and PFC. MAB was also able to prevent the reduction of GSH levels in the HIP.

Conclusion: The results indicated that MAB is a compound with a potential antidepressant activity that also acts to combat oxidative damage.

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About SBNP

The first edition of the Brazilian Symposium of Neuropsychoparhamacology (I Simpósio Brasileiro de Neuropsicofarmacologia, I SBNP) was held at the School of Medicine of Ribeirão Preto, University of São Paulo (FMRP-USP), on September 2014, where more than 150 participants, including researchers, clinicians and students, from Brazil and abroad, presented their work and discussed many different aspects on Neuropsychopharmacology. The positive evaluation of I SBNP by the participants, which also manifested interest in joining its second edition, associated to the increasing need in integrating students and researchers working on basic and clinical aspects of Neuropsychopharmacology motivated the organization of the II SBNP.

With the important support from the Brazilian Council for Science and Technology (CNPq), followed by funding agencies and organizations from Brazil and abroad (see bellow), the II SBNP now takes place in Florianópolis, at the Federal University of Santa Catarina (UFSC). As the first one, the II SBNP aims to create a scientific environment for integrating researchers from different Universities and research centers working on neuropsychopharmacology in Brazil and abroad; to provide an environment where researchers can present results from basic and clinical neuropsychopharmacology and engage in high level scientific discussions in the field; to provide a distinguished scientific program to students, researchers and professionals working on neuropsychopharmacology; to support and increase the interest on neuropsychopharmacology amongst graduate and undergraduate students.

Therefore, SBNP aims to stimulate the dialogue between researchers of different fields and backgrounds in neuropsychopharmacology to contribute with a better comprehension of mental and neurological disorders as well as foster the development of novel treatment options.

Thank you for your participation!

The Organizing Committee

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