Setor 03. Psicofarmacologia/Psychopharmacology

03.001

The anxiogenic properties of pentylenetetrazole as an unconditioned stimulus to promote olfactory fear conditioning in rats. Cavalli J, Bertoglio LJ, Carobrez AP UFSC - Farmacologia

Introduction: Animals display anxiety and fear when challenged to dangerous threatening situations at risk to their integrity. Although fear to certain kinds of stimuli is unconditionally hardwired, it can also result from classical fear conditioning. In this context, exteroceptive cues such as footshocks are often employed as unconditioned stimulus (US), but organismic interventions are also able to modify the animal internal mood, and thus could be used as US either as a single interoceptive or combined with an exteroceptive cue. The association of five footshocks with a neutral odor is able to establish an olfactory fear conditioning (OFC) in rats (Kroon & Carobrez, 2009). The present study sought to investigate whether the anxiogenic-like effect of pentylenetetrazole (PTZ) would turn the neutral coffee-odor into a conditioned stimulus in the OFC paradigm. **Methods:** The protocol used in experiment 1 to promote OFC comprised two consecutive phases: acquisition (2 days) and expression (3 days). The acquisition phase was executed in a chamber connected to a shock generator. On day 1, male Wistar rats aged three-months were familiarized to the apparatus. On day 2, they received a systemic injection of PTZ (15 mg/kg i.p.) or saline associated with 0 or 3 pairings of footshock (0.4 mA/2s; 30 s inter-trial period) in the presence of coffee-odor (first-order conditioned stimulus; CS1). The expression phase was performed in an odor box comprising an open and an enclosed communicating compartment, and consisted of 3 consecutive sessions lasting 10 min each one: familiarization (day 3; neutral odor); CS1-test (day 4; coffee-odor) and second-order CS (CS2)-test (day 5; neutral odor). Behavioral measures scored on CS-1 and CS-2 tests were the percentage of time approaching the coffee-odor (%AT) and the percentage of time hiding in the enclosed compartment (%HT). All procedures were approved and conducted in agreement with the Animal Ethics Committee (23080.006118/2004-36/UFSC). **Results:** ANOVA followed by Newman-Keuls test ($p<0.05$) revealed that rats paired with PTZ-coffee-odor decreased the %AT (controls = 25±3; PTZ/coffee-odor = 14±2) and increase the %HT (controls = 45±3; PTZ/coffee-odor = 70±4). When 3 footshocks were added during this pairing, defensive behaviors scored were greater than before. Pretreatment via i.p. with 0.5 mg/kg of the benzodiazepine midazolam (MDZ) fully counteracted their expression (%AT: PTZ/coffee-odor/saline = 11±5; PTZ/coffee-odor/MDZ = 20±3; %HT: PTZ/coffee-odor/saline = 78±9; PTZ/coffee-odor/MDZ = 57±5). Moreover, after being paired with PTZ, alone or combined with footshocks, the coffee-odor was able to promote a new fear conditioning related to the context where it was re-exposed (CS2) as revealed by a reduction in %AT (controls = 24±5; coffee-odor/context = 13±2) and an increase in %HT (controls = 51±6; coffee-odor/context = 69±4). **Conclusion:** The results show that PTZ is able to succeed as an aversive US in the OFC and that MDZ, at an anxiolytic-like dose, reduces the expression of the rat's defensive behavior due to the previous conditioning. **Financial support**: CNPq, CAPES, FAPESP, FAPESC, UFSC. **References**: (1) Kroon J.A., Carobrez A.P., 2009. Olfactory fear conditioning paradigm in rats: Effects of midazolam, propranolol or scopolamine. *Neurobiol Learn Mem* 91, 32-40.

03.002

Agmatine prevents social recognition memory impairments in mice submitted to intranasal MPTP model of Parkinson's disease. Matheus FC[1], Rial D[1], Aguiar Jr AS[1], Santos ARS[4], Prediger RD[1] [1]UFSC - Farmacologia, [2]UFSC - Ciências Fisiológicas

Introduction: Agmatine is an endogenous polyamine that has been considered a novel neuromodulator in the CNS with neuroprotective properties. Considering that the management of motor and non-motor symptoms of Parkinson's disease (PD) remains a challenge, here we investigated the preventive effects of agmatine in C57BL/6 mice infused with a single intranasal (i.n.) administration of the proneurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (1 mg/nostril), a valid animal model of the early stages of PD. **Methods**: Fifteen-month-old female C57BL/6 were chosen since they are more susceptible to the neurotoxic effects of MPTP and they were divided in four groups: control + control (Cont/Cont), agmatine + control (agmatine/Cont), control + MPTP (Cont/MPTP) and agmatine + MPTP (agmatine/MPTP). The agmatine treatment (30 mg/kg, i.p.) was conducted once daily during five consecutive days. One hour after the last injection of agmatine the proneurotoxin MPTP (1 mg/nostril) was infused intranasally. Animals were evaluated in locomotor (open field) and cognitive (social recognition) tasks 7 days after MPTP infusion. CEUA-UFSC: PP00111. **Results and discussion**: No differences were observed in locomotor activity among treatment groups. In the social recognition task, MPTP-treated mice spent as much time investigating the juvenile mouse during the second encounter as they did in the first exposure, reflecting a clear impairment of the juvenile's recognition ability. More importantly, adult mice previously treated with agmatine and infused with MPTP, behaved in a similar way to control-treated mice, i.e. they were able to recognize the juvenile mouse after an interval of 30 min. These results indicate, for the first time, that agmatine improves the short-term social memory deficits induced by MPTP in mice, suggesting that agmatine may represent a useful tool in the prevention of cognitive impairments associated to PD. **Financial support**: CNPq, CAPES, FAPESC and FINEP.

03.003

Acquisition of olfactory fear conditioning by beta-adrenergic receptor activation of the dorsal premammillary nucleus in rats. Pavesi E[1], Canteras NS[2], Carobrez AP[1] [1]UFSC - Farmacologia, [2]USP - Anatomia

Introduction: Beta-adrenergic receptors (BAR) within the dorsal premammillary nucleus (PMd) have been shown to mediate defensive responses (DR) toward predator odor (1). Furthermore, PMd has also been demonstrated to mediate DR resulting from shock-odor paired conditioning (2). The BAR antagonist, atenolol, applied to the PMd was able to reduce the defensive behavior elicited by either the unconditioned (US) predator odor or the olfactory fear conditioning (OFC) stimulus. The OFC generally occurs after the pairing of an US exteroceptive stimulus (footshock) with a neutral odor (amyl acetate; AA) (3). It remains to be tested whether an interoceptive stimulus, such as, the BAR activation within the PMd could be used as an US to induce the OFC. To test this hypothesis, rats were conditioned by pairing intra-PMd microinjection of the BAR agonist, isoproterenol (ISO) with AA odor and the magnitude of the DR exhibited in the presence of the olfactory conditioned stimulus (CS1) and in a subsequent re-exposition to the context (CS2) was taken as a measure of the OFC. **Methods**: Seven days after male Wistar rats had received a guide cannula aimed at the PMd, they were submitted to the OFC protocol consisting of 2 consecutive phases: the acquisition (2 sessions) and the expression (3 sessions). All the sessions were spaced 24 hours each other within 5 consecutive days. On day 1, rats were familiarized with the conditioning chamber. On the following day, they received microinjections (0.3μl) of PBS or ISO (10 or 40nmol) 5 min before the AA exposure (CS1 -250 μl AA 5%). The total exposure time to the AA was 10min. The OFC expression phase was set in an odor box comprising an open and an enclosed communicating compartment. The sessions were: familiarization to chamber (neutral odor); CS1 test (AA odor) and CS2 test (neutral odor). The percentage of time the rats spent near the odor source (%AT), or in the hidden compartment (%HT) during 10 min for each session were taken as an index of DR. The protocols were approved by the Animal Ethics Committee 23080.055752/2006-64-UFSC. **Results:** ISO induced the acquisition of OFC (ANOVA, $F(6,72)=10.7$, $p<.05$). Rats exposed to AA during 10min showed a significant decrease in the %AT (ISO10: 10.6±1.9; ISO40: 9.2±1.5) and increased %HT (ISO10: 76.3±4.6; ISO40: 78.5±3.0) during the CS1 session when compared to subjects from the PBS (%AT=30.1±3.4; %HT=37.5±4.4) group. The same profile of results was obtained during the CS2 session [PBS (%AT=28.5±3.8; %HT=36.1±6.1); ISO10 (%AT=10.7±1.9; %HT=72.1±4.0); ISO40 (%AT=10.0±1.4; %HT=73.6±2.0)]. **Discussion and Conclusions:** Taken together, the present findings demonstrate that BAR activation in the PMd, functioning as an interoceptive-US, promote a robust CS-US association, in addition to its well known effects in the expression of OFC. The results suggest the OFC paradigm as an experimental tool to test various compounds and/or brain structures responsible to either promote fear conditioning or reduce the expression of DR. **References**: (1) Do Monte et al., *J Neurosci*., 28:13296, 2008. (2) Canteras et al., Neurosci Biobehav Rev., 32:1228, 2008. (3) Kroon & Carobrez. Neurobiol Learn Mem., 91:32, 2009. **Financial Supports:** CNPq, CAPES, FAPESP, UFSC

03.004

Chemical stimulation of the dorsolateral periaqueductal gray matter enhances fear conditioning responses. Mochny CR[1], Kincheski GC[1], Molina VA[3], Carobrez AP[1]
[1]UFSC - Farmacologia, [2]CONICET - Farmacologia

Introduction: The dorsolateral periaqueductal gray matter (dlPAG) is an integrative area of the neuroaxis involved in the modulation of appropriate defensive behavior. Rats chemically stimulated with n-methyl-d-aspartate (NMDA) into the dlPAG exhibit defensive responses such as running, jumping, freezing and avoidance. Preexisting state of fear or anxiety may contribute as evolutionary interoceptive stimulus to potentiate animals fear eliciting responses. Therefore, the present study was outlined to test the hypothesis that the aversive state induced by the chemical stimulation of dlPAG may contribute to enhance fear conditioning responses resulting from footshock-context pairing. **Methods**: One week before the experimental procedures, male *Wistar* rats weighing 300-450g were implanted with guide cannulas aimed at the caudal dlPAG. On day 1, the subjects were submitted to 3 footshocks (0.5 mA, 3s duration, 30s apart), in a shock chamber. On day 2 (24h after), the rats received either NMDA (100 pmol) or PBS microinjection (0.2μl) into the dlPAG and were placed inside a polypropylene box for 10 minutes. On day 3, the subjects were re-exposed to the same shock chamber during 3 minutes (test session) and the defensive behavior represented by the % freezing time was scored. The protocols were approved according to the Animal Ethics Committee (23080.0055752/2006-64/UFSC). **Results:** An increased %freezing time for the group receiving NMDA 100 pmol into dlPAG (74.52 ± 2.85%) when compared to the PBS group (23.33 ± 14.68%) during the test session, was confirmed by the statistical analysis performed using the unpaired t test [$t(9)=4.52$; $p<0.005$]. Conclusions: The interoceptive stimulation due to the chemical stimulation of dlPAG with NMDA was able to enhance the %freezing time resulting from the footshock-context fear conditioning. The results showing that the increased aversive state generated from dlPAG activation potentiate the fear eliciting response, support the suggestion that the emotional processes underlying the dlPAG activity can interfere with higher cognitive processes. Financial support: CAPES, CNPq, FAPESC, UFSC, FAPESP.

03.005

Estudos preliminares do efeito hipnótico e anticonvulsivante de *Bourreria huanita* em modelos farmacológicos específicos. Cattani D[1], Corso M[1], Perondi DM[1], Zanella S[1], Cechinel-Filho V[1], Cruz SM[2], Torres MF[2], Cáceres A[2], De-Souza MM[1] [1]NIQFAR-CCS-UNIVALI, [2]Universidad de San Carlos - Ciencias Químicas y Farmacia

Introdução: A espécie *Bourreria huanita* (La Llave & Lex) Hemsl. pertencente a família Boraginaceae é popularmente conhecida na Guatemala como *esquisuchil* e "flor del Hermano Pedro". O chá da flor é utilizado na medicina popular Guatemateca em doenças do Sistema Nervoso Central**.** O objetivo do presente estudo foi estudar as possíveis propriedades hipnóticas e anticonvulsivantes do extrato hidroalcoólico 50% (EH) obtido da flor de *B. huanita* em modelos farmacológicos *in vivo*, utilizados no *screening* pré-clínico de substâncias psicotrópicas. **Métodos:** Foram utilizados camundongos *Swiss Webster* machos (25-30g), oriundos do Biotério Central da UNIVALI. Os protocolos experimentais foram submetidos ao CEP da UNIVALI e aprovados sob parecer 475/08. A atividade anticonvulsivante do EH foi avaliada através do modelo de convulsão induzido por pentilenotetrazol (PTZ/ 80 mg/kg, i.p.) MCPTZ). Os animais receberam tratamento com o EH (50-150 mg/kg, v.o.) veículo (VEIC, salina, 0.1mL/10g) e fenobarbital (FEN-40mg/kg) e 1h após a convulsão foi induzida. Durante 60 min foi cronometrada a latência para a primeira crise convulsiva bem como o número de óbitos e o tipo de crise observada. A atividade hipnótica do EH foi avaliada através do modelo de indução do sono por barbitúricos (MSB). Os animais foram tratados com o EH, veículo, e diazepam (DZP- 1mg/kg) e 1 h após receberam pentobarbital sódico (PEN- 50mg/kg, i.p.). Imediatamente após a aplicação do PEN foi cronometrado para cada animal a latência para o sono LPS e o tempo total de sono (TTS) do hipnose (modelo de indução do sono por barbitúricos); deambulação motora (modelo Campo Aberto, *Open Field*). Os efeitos do EH sobre a deambulação dos animais foram verificados através do modelo do Open Field (MOF). Os animais receberam os tratamentos acima e foram colocados no MOF durante 6 minutos, durante os quais foi avaliado o número de *rearings* (NR= postura de exploração) e o número de *crossings* (CR= cruzamentos). **Resultados:** No MCPTZ o EH da planta foi ineficaz em proteger os animais da crise convulsiva (EH = 49,0 ± 12) quando comparado ao controle (VEIC 59,0 ± 9,3) sendo esse efeito observado com o tratamento de FEN (75 ± 15). O EH não protegeu os animais da letalidade induzida por PTZ tendo 100% de óbitos e, houve 100% de crises do tipo tônica. No MSB observou-se de forma significante a diminuição da LPS (VEIC/ 448,0 ± 1,33; EH/ 258,0 ± 12,50; DZP/.257 ± 29) e aumento do TTS (VEIC/ 282 ± 6,4; EH 355 ± 5,90). No MOF, o extrato promoveu aumento do número de *crossings* de forma significativa (VEIC/ 106 ± 15; EH/ 125 ± 21) bem como o número de *rearings* (VEIC; 42,0 ± 7,0; EH/ 68 ± 10). **Conclusão:** Os resultados em conjunto nos permitem concluir que o EH da planta em estudo, nas doses testadas, não exibe efeito anticonvulsivante. Também foi observado que o mesmo não promove efeito sobre a deambulação dos animais, não comprometendo, portanto o sistema motor dos mesmos. Entretanto, o EH exibiu efeito hipnótico nos animais, validando seu uso popular no tratamento da insônia. Apoio: Rede 0284 RIBIOFAR/CYTED/CNPq e UNIVALI.

03.006

Avaliação do efeito ansiolítico e antidepressivo de *Bourreria huanita* em modelos farmacológicos específicos. Corso M[1], Cattani D[1], Perondi DM[1], Zanella S[1], Cechinel-Filho V[1], Cruz S M[2], Torres M F[2], Caceres A[2], De-Souza M M[1] [1]NIQFAR-CCS-UNIVALI Farmácia, [2]Universidad de San Carlos - Ciencias Químicas y Farmacia

Introdução: Na medicina popular guatemateca *Bourreria huanita* (La Llave & Lex) Hemsl. tem sido utilizada como agente ansiolítico, antidepressivo e hipnótico. Essa planta pertence à família Boraginaceae e é popularmente conhecida como "esquisuchil" e "flor del Hermano Pedro". O objetivo do presente estudo foi estudar as propriedades farmacológicas da planta no Sistema Nervoso Central utilizando extrato hidroalcoolico 50% (EH) obtido da flor da mesma em modelos farmacológicos *in vivo*, utilizados no *screening* pré-clínico de substâncias psicotrópicas. **Métodos:** Os protocolos experimentais foram submetidos ao CEP da UNIVALI e aprovados sob parecer 475/08. Nos experimentos foram utilizados camundongos machos (25-30g, N= 8-12) obtidos do Biotério Central da UNIVALI. Para detectar o efeito ansiolítico do EH foi utilizado como modelo de ansiedade o labirinto em cruz elevado (LCE), sendo avaliados nesse modelo o efeito do EH (50-150mg/kg, v.o.), veículo (VEIC = salina, 0,10mL/10g e diazepam (DZP, 0.75mg/kg, i.p.) sobre os parâmetros de freqüência de entradas nos braços abertos (FEA) e fechados (FEF) e tempo de permanência nos braços abertos (TPA) e fechados (TPF) durante 5 minutos . Para avaliar o efeito antidepressivo do EH foi utilizado o modelo do nado forçado (MNF), durante o qual foi avaliado os efeitos do EH veículo e imipramina (IMI, 5.0 mg/kg) sobre parâmetros comportamentais como os tempos de agitação (TAG) e imobilidade (TIM) durante 6 minutos. Também foi realizado o teste de deambulação, o modelo do Open Field, (MOF) por 6 minutos, durante os quais foi avaliado os efeitos do EH e veículo sobre o número de cruzamentos (*crossings*) e número de atividades exploratória (*rearing*). Os animais foram tratados com o extrato em diferentes concentrações (100 e 150mg/kg), por via oral, e avaliados 60 minutos após o tratamento nos modelos acima citados. **Resultados:** ANOVA seguida pelo teste Dunnet ($p<0,05$) demonstrou que houve um aumento na porcentagem do TPA nos animais que receberam o EH e o diazepam (VEIC/ 30 ± 13; EH (150mg) /59 ± 11; DZP/72.23 ± 8.4) quando comparado com o controle. Também observou-se aumento na FEA com o tratamento com o EH e o controle positivo (VEIC/ 34 ± 12.80; EH 150mg/kg; 52 ± 13; DZP/64± 13). A mesma dose do extrato e do controle positivo no MNF produziu diminuição do TIM quando comparado com o controle (VEIC/120 ± 17; EH/ 93 ± 14; IMI / 34± 3,35). No MOF, o extrato promoveu aumento do número de crossings de forma significativa (VEIC/ 106 ± 15; EH/ 125 ± 21) bem como o número de rearings (VEIC; 42,0 ± 7,0; EH/ 68 ± 10). **Conclusão:** Os resultados, embora preliminares, permitem concluir que a planta em estudo exibe efeito ansiolítico e antidepressivo em animais, validando em parte o uso popular no tratamento da ansiedade e depressão. Outros experimentos serão necessários para determinação dos constituintes químicos responsáveis por tais efeitos farmacológicos bem como seus respectivos mecanismos de ação. Apoio: Rede 0284 RIBIOFAR/CYTED/CNPq e UNIVALI.

03.007

Temporal analysis of olfactory fear conditioning consolidation in rats. Medeiros TF, Do Monte FHM, Kroon JA, Carobrez AP UFSC - Farmacologia

Introduction: A fearful experience can establish an emotional memory that results in behavioral changes. The association between an odor, as a conditioned stimulus (CS), and electrical footshock, as an unconditioned stimulus (US), is an effective model to study fear-induced behavior. Fear memory is characterized by acquisition and consolidation phases. Consolidation stage involves the conversion of labile memory into permanent memory, and this process is dependent of protein synthesis. Studies have shown that administration of protein synthesis inhibitors prevent the consolidation of aversive memories. Thus, the present study evaluated the temporal effect of cycloheximide (CHX) treatment- an inhibitor of protein synthesis - in the aversive olfactory memory consolidation by using the olfactory fear conditioning paradigm. **Methods:** Protocols comprised two phases performed 7 days apart: the acquisition (US+CS pairing) and the expression of conditioning emotional response (CER). The acquisition phase consisted of two sessions in a chamber connected to a footshock generator. On day 1, male *Wistar* rats were placed in the conditioning chamber and allowed to explore freely the apparatus. On day 2, subjects received five pairings of footshock (40 s inter-trial period; 0.4 mA/2s) in the presence of amylacetate odor (CS). Animals were injected with saline or CHX (1 mg/kg, IP) before, immediately after or 3 hours after the olfactory conditioning protocol. The expression of CER was evaluated in an odor box comprising an open and an enclosed communicating compartment. This phase consisted of two sessions: familiarization (neutral odor) and test (CS exposure), in which the %time spent near the odor source (%approach time; %AT) and %time in the enclosed compartment (%hide time; %HT) were used as indexes of defensive behavior during 10 minutes of exposure. All protocols were approved according to the Animal Ethics Committee (23080.055752/2006-64-UFSC). **Results:** Statistical analysis revealed a significant ($P<0.05$) decrease in %AT (4.2±1.3) and increase in %HD (86.0±3.4) in the odor-paired group when compared to non-paired group (%AT=13.4±2.5; %HT= 56.0±3.6) during test session. The odor-paired group treated with CHX immediately after the conditioning exhibited a reduction in the defensive behavior characterized by an increased %AT (17.6±2.9) and a reduced %HT (56.9±2.5) parameters when compared to saline-control-group (%AT=7.9±1.7; %HD=76.4±3.7). No effects were observed in the subjects injected with CHX 30 min prior or 3 hours after the conditioning session. **Discussion:** The results showed that five associations between amylacetate odor and electric footshock were able to promote a robust CER when the animals were re-exposed to the olfactory stimulus in a different context 7 days after the conditioning session. Furthermore, consolidation of olfactory fear memory seems to be dependent of protein synthesis, a process initiating immediately after the olfactory conditioning session until 3 hours later. **Financial Support:** CAPES, CNPq, PIBIC-UFSC, FAPESP, FAPESC.

03.008

Inhibition of nNOS and sGC in the dorsal hippocampus induces antidepressant-like effects in rats. Sales AJ[1], Guimarães FS[2], Joca SR[1] [1]FCFRP-USP Física e Química [2]FMRP-USP

Introduction: Recent evidences have suggested that nitric oxide (NO) might be involved on the neurobiology of depression, since NO synthesis inhibition induces antidepressant-like effects in different animal models. Considering that intra-hippocampal injection of NO synthase (NOS) inhibitor induces antidepressant-like effects in rats, it is believed that increased hippocampal levels of NO in response to stress exposure might trigger the development of depressive-like behaviors. However, the participation of specific NOS isoforms and of the soluble guanylyl cyclase (sGC), the principal target for NO, in such effects remains to be investigated. Therefore, the aim of the present study was to investigate the involvement of hippocampal nNOS-sGC pathway in the modulation of the depressive-like behavior in the forced swimming test in rats. **Methods:** Seven days after the stereotaxic surgery, male Wistar rats (n = 6-12/group) with guide-canulas aimed at the dorsal hippocampus were submitted to pretest (PT: 15 min of forced swimming) and, immediately after, they received a local microinjection of n-propyl-L-arginine (NPA, selective nNOS inhibitor: 0.001, 0.01 or 0.1 nmol/0.5 µL), 1400W (selective iNOS inhibitor: 0.001 nmol/0.5 µL), ODQ (sGC inhibitor: 0.1, 1.0 or 10 nmol/0.5 µL) or saline (0.5 µL). Twenty four hours later, the immobility time were registered at a 5 min swimming test. All protocols described herein have been approved by a local ethical committee (Proc. N. 08.1.1133.53.4). **Results**: NPA, but not 1400W, significantly reduced the immobility time in the FS test (vehicle: 134.4 ± 14.95, 0.001 nmol: 27.4 ± 12.14, 0.01 nmol: 56.1 ± 21.8, 0.1 nmol: 23.64 ± 11.02, 1400W: 131.0 ± 29.83; $F_{4,47} = 10.43$, $p<0.001$). Intra-hippocampal ODQ injection also reduced the immobility time (vehicle: 164.0 ± 22.43, 0.1 nmol: 137.3 ± 31.6, 1.0 nmol: 12.57 ± 5.69, 10 nmol: 110.0 ± 37.41; $F_{3,21} = 7.88$, $p<0.01$), an antidepressant-like effect in this animal model. **Discussion**: The present results indicate that inhibition of nNOS and sGC in the hippocampus induces antidepressant-like effects. However, iNOS inhibitor administration at an equimolar dose (0.001) did not induce any significant effect, confirming that nNOS is preferentially involved in the response (Ki iNOS NPA/1400W: 25714). Therefore, it suggests that stress leads to nNOS activation and NO synthesis in the hippocampus, what may trigger sGC activation and subsequent behavioral consequences, such as the depressive-like behavior. **Financial Support:** CNPq, FAPESP.

03.009

Hippocampal DNA methylation regulates depressive-like behavior in rats. Sales AJ[1], Gomes MVM[2], Joca SR[1] [1]FCFRP-USP - Física e Química, [2]FMRP-USP - Puericultura e Pediatria

Introduction: Recent studies have implicated epigenetic modification in the formation of stable neuronal adaptations in the hippocampus that might underlie some of the long lasting changes in behavior which are induced by chronic stress and reversed by antidepressant drugs. For example, antidepressant treatment induces histone acetylation in the hippocampus, which is associated with transcriptional activation of specific genes, whereas stress increases DNA methylation, which is associated with transcriptional repression. Moreover, higher levels of methylation at specific genomic loci have been found in the hippocampus of people who committed suicide. Since the involvement of DNA methylation in the regulation of depressive-like behaviors is not yet known, we aimed at investigating if increasing hippocampal gene expression through the local inhibition of DNA methyltransferase (DNMT), the enzyme responsible for DNA methylation, would induce antidepressant-like effects in the forced swimming (FS) test in rats. **Methods:** seven days after the stereotaxic surgery, male Wistar rats (n= 6-8/group) with guide-canulas aimed at the dorsal hippocampus were submitted to pretest (PT: 15 min of forced swimming) and, immediately after, they received a local microinjection of decitabine (DNMT inhibitor: 50, 100 or 200 nmol/0.5 µL) or saline (0.5 µL). Twenty four hours later, the immobility time were registered at a 5 min swimming test. An independent group of rats were submitted to the same behavioral procedures but received 3 ip injections (0, 5 and 23h after PT) of vehicle (1 mL/kg) or fluoxetine (10 mg/kg), as a positive control of the antidepressant-like effect. All protocols described herein have been approved by a local ethical committee (Proc. N. 08.1.1133.53.4). **Results:** Decitabine reduced the immobility time in the FS test (vehicle: 159.9 ± 15.40, 50 nmol: 116.0 ± 27.17, 100 nmol: 69.29 ± 14.5, 200 nmol: 147.5 ± 9.2; $F_{3,28}$ =3.59, $p<0.05$), an effect that was significant at the dose of 100 nmol (Dunnets, $p<0.05$). Fluoxetine also reduced the immobility during the test (vehicle: 150.0 ± 33.09, fluoxetine: 54.00 ± 11.64, t_{12} = 3.06, $p<0.05$), an antidepressant-like effect in this animal model. **Discussion:** The present results indicate that DNA methylation inhibition in hippocampal cells induces antidepressant-like effects, similarly to fluoxetine, a prototype antidepressant. Therefore, stress-induced methylation and subsequent transcription repression of specific genes in the hippocampus might mediate the development of depressive-like behaviors. Further experiments are under development to identify the candidate genes which expression is the under control of such epigenetic mechanism during stress. **Financial Support:** CNPq, FAPESP**.**

03.010

Ethanol withdrawal results in a decreased locomotor activity and FOS expression in distinct brain areas of rats. Bonassoli VT, Oliveira RMMW, Milani H UEM - Farmácia e Farmacologia

Introduction: Ethanol addiction has been conceptualized as a progression from occasional, impulsive use up to compulsive behavior, and its withdrawal causes many effects. Despite many things be known about ethanol withdrawal, the neural substrate underlying the effects induced by ethanol abstinence is still unclear. We used the immunohistochemistry technique to detect Fos protein and then visualize neurons that could be activated by ethanol withdrawal. The aims of this study were two-fold: (*i*) to assess how ethanol abstinence affects the locomotor behavior measured in the open field, and (*ii*) to examine the expression of the Fos protein in various brain regions. **Methods:** Thirty-three, male Wistar rats were divided in three groups (n=11 each). Two groups received a 6–8% (v/v) oral ethanol self-administration offered in a balanced solution diet (Sustagen M®, chocolate flavor, Mead Johnson) for a period of 21 days, followed by abrupt discontinuation of the treatment. The third (control) group received the same dietary base added with sucrose, but without ethanol, for similar periods of time. Passed 24 or 48 hours after discontinuation of the ethanol-containing diet, both the first and second groups, respectively, were tested for 10 min. in the open field. The control animals were tested immediately after the end of the treatment. The animals behaviors were videotaped and analysed with the help of Ethovision software for measurement of exploratory activity. After behavioral testing, the animals were euthanized and the brain removed for Fos protein immunohistochemistry. Behavioral and histological data (mean±SEM) were quantified by one-way analysis of variance (ANOVA) followed by the Tukey's test. The experimental procedures were approved by the Ethics Committee on Animal Experimentation of UEM (CEEA 003/2008). **Results and Discussion**: Locomotion, as measured by the distance travelled into the open field, was decreased in the group tested 24 h after ethanol withdrawal, (control: 4.610,2 ± 471,9; ethanol: 2.785,0 ± 507,2; $F_{2,32}$=4,07, $p<0.05$.). In contrast, locomotion was not significantly affected in the group tested 48 h after ethanol withdrawal (ethanol: 3579,1 ± 403,9; $p>0.05$ vs. control). Twenty-four hours of alcohol withdrawal induced a robust increase in Fos expression in lateral hypothalamus ($F_{2,7}$=6.6; $p<0.05$), dorsomedial ($F_{2,7}$=17.5; $p<0.05$) and dorsolateral periaquedutal grey matter ($F_{2,7}$=7.03; $p<0.05$). Just a tendency for increased Fos immunoreactivity was observed in the ventral diagonal band and *substantia nigra* ($p<0.05$). In conclusion, 24 h of ethanol withdrawal reduced locomotor activity, an effect that was parallel to an increased Fos expression in brain areas related to emotional behavior. Further experiments are needed to understand the neural substrates affected by ethanol withdrawal and the behaviors related to them. This study was supported by UEM and CAPES.

03.011

Effect of dopamine and nitric oxide systems manipulation on spontaneous prepulse inhibition disruption of *wistar* rats. Issy Pereira AC[1], Lazzarini M[2], Del Bel EA[3] [1]FMRP-USP - Farmacologia, [2]USP - Neurologia, [3]FORP-USP - Morfologia, Estomatologia e Fisiologia

Introduction: Cognitive and attentional deficits in schizophrenia include impairment of the sensory filter input as measured by prepulse inhibition (PPI) reaction. Disruption of PPI can be induced by dopaminergic agonists or transporter inhibitors [1]. However, nonpharmacological disrupted models of PPI have been encouraged as a possible predictive test for the screening of antipsychotic drugs. Nitric oxide (NO) modulates dopamine uptake and release processes and seems to be implicated in cognitive process and dopamine related pathologies [2,3]. **Objectives:** The aim of this study was first to analyze the spontaneous PPI disruption of *Wistar* rats as a nonpharmacological model of sensorimotor gating deficit and second to analyze the NO role on sensorimotor system. We investigated if the animals were sensitive to antipsychotics drugs, diazepam and NO inhibitors. We also analyzed the effect of dopamine depletion by lesion of medial forebrain bundle with the neurotoxin 6-hydroxydopamine (6-OHDA). **Methods**: Male *Wistar* rats with spontaneous PPI disruption were selected using our routine PPI session and received intraperitoneal injection (one hour before test) of saline or either antipsychotics [haloperidol (0.1, 0.3 or 1 mg/kg) and clozapine (0.5, 1.5 or 5 mg/kg)], or diazepam (1 or 3 mg/kg), or NO inhibitors, [N^G nitro L-arginine (LNOARG, 40 mg/kg, acute or subchronic, for 8 days) and 7-Nitroindazole (7NI, 3, 10 or 30 mg/kg)], and were submitted to PPI test. Nigrostriatal lesion was produced microinjecting 6-OHDA with 0.02% ascorbic acid (4 µl, 8 µg/µl) in 0.9% saline into the right medial forebrain bundle - Paxinos and Watson's rat brain atlas: anterior: −4.4 and lateral: −1.2 from bregma. The animals with nigrostriatal denervation did not receive any drug and were tested 21 days after 6-OHDA lesion. The PPI test consist of 64 trials irregularly divided into pulse (P, white noise, 100 dB), prepulse (pure tone; 3kHz; 69, 73 or 81 dB), prepulse+pulse (PP) and no-stimuli with white background noise level of 64 dB – %PPI=[100-(PP/P)*100]. The percentage of PPI was analyzed with repeated measures (MANOVA) with the treatment as the independent factor and the prepulse intensity as repeated measure. Duncan´s post hoc test ($p<0.05$) was used to specify differences revealed by significant MANOVAS. **Discussion:** Data suggests that *Wistar* rats with spontaneous PPI disruption may represents an interesting nonpharmacological model of sensorimotor deficit that can be used to evaluate new therapeutic strategies. Since both dopaminergic antagonism and dopamine depletion on nigrostriatal pathway increased the PPI response it is possible that these animals have disturbed dopamine function. NO may participate of sensorimotor control given that NO inhibitors reversed the spontaneous PPI disruption of *Wistar* rats in similar way of antipsychotics. **Results:** The disruption of PPI was reversed by the antipsychotics haloperidol [0.3 mg/kg (37±5.66; 15±3.22, 16±3.91) and 1 mg/kg (42±5.49; 16±4.65; 14±3.98) PP 81, 73 and 69 dB, respectively; $p=0.001$] and clozapine [5 mg/kg (21±4.09; 19±4.22; 16±3.05) PP 81, 73 and 69 dB, respectively; $p=0.002$] and NO inhibitors LNOARG [40 mg, acute (34±6.16) and subchronic (38±5.69); $p=0.046$] and 7NI [10 mg/kg (44±6.57; 16±6.2) and 30 mg/kg (41±8.18; 15±8.56) PP 81 and 69 dB, respectively; $p=0.003$], in contrast to diazepam that, as expected, did not modify PPI response ($p=0.42$). The dopamine depletion by 6-OHDA lesion also blocked the PPI disruption ($p=0.024$). 1. Geyer M.A., Krebs-Thomson K., Braff D.L., Swerdlow N.R. (2001) Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: a decade in review. *Psychopharmacology* 156: 117-154. 2.West AR, Galloway MP, Grace AA (2002) Regulation of striatal dopamine neurotransmission by NO: effector pathways and signaling mechanisms. *Synapse* 44:227–245. 3-Guix FX, Uribesalgo I, Coma M, Munoz FJ (2005) The physiology and pathophysiology of NO in the brain. *Prog Neurobiol* 76: 126–152. **Financial support:** FAPESP Ethnic committee number: 229/2005

03.012

Role of medial prefrontal cortex beta-adrenergic type 1 receptors on anxiety in rats.

Stern CAJ, Do Monte FH, Carobrez AP, Bertoglio LJ UFSC - Farmacologia

Introduction: The medial prefrontal cortex (mPFC) plays an important role in the control of anxiety and learning/memory. Indeed, laboratory animals with permanent mPFC lesions demonstrate less anxiety-related defensive behaviors and impaired learning acquisition. The neurochemical mechanisms underlying these functions, however, are still under investigation. Beta-adrenergic type 1 receptors are widely expressed throughout the central nervous system, including the mPFC [1]. The objective of the present study was to investigate whether the antagonism of beta-adrenergic type 1 receptors located within the mPFC would interfere with the behavioral performance of naive or experienced rats in the elevated plus-maze (EPM). It is worth mentioning that the EPM trial 1/trial 2 protocol has proven to be suitable to evaluate either anxiety or memory processes in the same animal [2]. **Methods**: Male Long-Evans hooded rats (Animal Ethics Committee: 23080.055752/2006-64 - UFSC) were bilaterally-implanted with guide cannulas aimed at the mPFC. One-week later, one group of rats was infused (0.2µl/side) into the mPFC with vehicle (phosphate buffered saline) or the selective beta-adrenergic type 1 antagonist atenolol (10 or 40 nmol) 10 min before the EPM trial 1. On the next day these groups were re-exposed (trial 2) to the EPM undrugged. Another group of rats was exposed to the EPM trial 1 undrugged, and 24 h later re-exposed (trial 2) to the EPM 10 min after the mPFC infusion of 40 nmol of atenolol. Behavioral measures scored during 5 min in both trial 1 and trial 2 were the percentage of open-arms time (%OAT), the percentage of open-arms entries (%OAE), stretched-attend postures (SAPs) and enclosed-arms entries (EAE). **Results:** Repeated-measures analysis of variance followed by Duncan test ($p<0.05$) showed an increase in both %OAT and %OAE in EPM-naive rats administered with 10 nmol (32 ± 8 and 69 ± 11, respectively) or 40 nmol of atenolol (30 ± 3 and 64 ± 7, respectively) when compared to controls (10 ± 3 and 23 ± 6, respectively). In EPM-experienced rats, however, the increase in open-arms exploration was no longer observed [%OAT = 6 ± 2 (controls), 6 ± 3 (atenolol 10 nmol) and 5 ± 1 (atenolol 40 nmol); %OAE = 24 ± 7 (controls), 42 ± 16 (atenolol 10 nmol) and 32 ± 13 (atenolol 40 nmol)]. In all cases, no statistically significant differences were observed for SAPs and EAE. **Discussion:** EPM-naive rats showed less open-arm avoidance than controls after the bilateral infusion of atenolol within the mPFC, indicating an anxiolytic-like effect. This atenolol effect was absent in EPM-experienced rats. These results suggest a role for beta-adrenergic type 1 receptors located in the brain region on regulating anxiety, but not memory. **Financial support**: CNPq, CAPES, FAPESC and FAPESP. **References:** (1) Rainbow TC, Parsons B, Wolfe BB. Quantitative autoradiography of beta 1- and beta 2-adrenergic receptors in rat brain. *Proc Natl Acad Sci* U S A. 1984 Mar;81(5):1585-9. (2) Carobrez AP, Bertoglio LJ. Ethological and temporal analyses of anxiety-like behavior: the elevated plus-maze model 20 years on. *Neurosci Biobehav Rev*. 2005;29(8):1193-205.

03.013

Effects of inhibition of neuronal nitric oxide synthase (nNOS) on FOS expression in the rat brain. Silva M[1], Aguiar DC[1], Guimarães FS[1], Joca SR[2] [1]FMRP-USP - Farmacologia, [2]FCFRP-USP - Física e Química

Introduction: Depression is one of the most prevalent psychopathologies in the world and one of the factors that may trigger this condition is stress. A large number of neurotransmitters have been proposed to be involved in the physiopathology of depression, including serotonin and, more recently, Nitric Oxide (NO). For example, the inhibition of nNOS, the enzyme that synthesizes NO, induces antidepressant-like effects in animal models, such as the forced swimming test (FST) (Yildiz et al., Psychopharmacology, 149:41-44, 2000) . However, the involvement of specific brain structures in such effects has not been studied yet. Therefore, we aimed at investigating the brain pathways involved in nNOS inhibition-induced antidepressant-like effects through the analysis of Fos protein expression, a marker of neuronal activity. Moreover, recent evidences have suggested that the aforementioned antidepressant-like effect is dependent on serotonin levels in the brain. (Harkin et al., Neuropharmacology, 44:616-623,2003). In order to test this hypothesis, the effects induced by a preferential nNOS inhibitor (7-NI) on Fos expression was compared with the effects induced by serotonin (Fluoxetine) and serotonin-noradrenaline (venlafaxine) reuptake inhibitors, prototype antidepressants. **Methods:** Male Wistar rats (200-220 g) were submitted to a forced swimming for 15 min (pre-test) and received three ip injections (0, 5 and 23h after PT) of Fluoxetine (FLX, 10 mg/kg), Venlafaxine (VLX: 10 mg/kg), 7-NI (30 mg/kg) or respective vehicles (1mL/kg). Twenty four hours later, rats were allowed to swim for 5 min (test), when immobility time was recorded. An independent group of animals received the same treatments or no treatment and was sacrificed three hours after the last injection to have their brain removed and processed for Fos immunohistochemistry (IHC). The number of Fos-positive nuclei per region was counted using a computerized image analysis system. All protocols described herein were approved by a local ethical committee (CETEA, Prot. N. 145/2008). **Results**. Treatment with FLX, VLX or 7-NI reduced the immobility time in the FST (Mean Diff. VLF: - 68,78; FLX : - 28,28; 7NI: - 47,04) ($F_{4,35} = 2.66$, $p<0.05$), an antidepressant-like effect in this model. For the Fos IHC, the following neuroanatomical sites were examined: cingulated, infralimbic and prelimbic cortices, the medial amydaloid nucleus (MeAmyg), the dorsolateral periaqueductal gray (DLPAG), the dorsal (DRN) and median (MRN) raphe nuclei, and the paraventricular nuclei of the hypothalamus (PVN). There were differences in Fos expression among structures, but no significant changes were induced by the treatments in any of the structure analyzed up until now. **Discussion and Conclusions**: Treatment with 7-NI induced antidepressant-like effect in the FST, similarly to FLX and VLX. In non-stressed animals, no significant difference was observed on Fos expression. Further studies are under development to investigate the effects induced by these drugs on FST-induced Fos expression in the rat brain. **Financial Support:** CNPq, FAPESP, FAEPA.

03.014

Involvement of the L-arginine-nitric oxide-CGMP pathway in the antidepressant-like effect of mirtazapine in the forced swimming test. Zomkowski ADE, Engel D, Gabilan NH, Rodrigues ALS UFSC - Bioquímica

Introduction: Mirtazapine, a drug used for the treatment of depression enhances noradrenergic and serotonergic neurotransmission (Peña et al., *Int. Immunopharmacol*. 5: 1069, 2005). We have demonstrated that the administration of mirtazapine by intraperitoneal (i.p.) route reduced the immobility time in the forced swimming test (FST) and tail suspension test in mice (XXI Reunião Anual da FeSBE, nº 13.031, 2006). The present study was aimed at investigating the effect of mirtazapine administered by oral (p.o.) route in the FST in mice. Moreover, the involvement of the L-arginine-nitric oxide-cGMP in the antidepressant-like effect of mirtazapine in the FST was also studied. **Methods:** Female Swiss mice (30-40 g, n = 6/group) were used**.** The experiments were performed after approval of the protocol by the Institutional Ethics Committee (PP185). The FST was carried out in mice individually forced to swim in an open cylindrical container (diameter 10 cm, height 25 cm), containing 19 cm of water at 25 1C. The immobility time in a 6-min session in the FST was registered. Mirtazapine was administered by p.o. route (0,3; 1; 3 e 10 mg/kg) 60 min before the FST. In order to rule out non-specific locomotor activity, mice were submitted to the open-field test. Comparisons between treatment groups and control were performed by ANOVA followed by Tukey's HSD test when appropriate. A value of $P<0.05$ was considered to be significant. **Results:** The administration of mirtazapine at doses of 1, 3 and 10 mg/kg, p.o. significantly reduced (78,81±7,2, 53,95±6,3 e 65,5±5,7, respectively) the immobility time in the FST as compared to the control (100%). These doses of mirtazapine did not produce any change in ambulation in the open-field test. The pre-treatment of mice with L-arginine (750 mg/kg i.p., a nitric oxide precursor) or sildenafil (5 mg/kg, i.p., a phosphodiesterase 5 inhibitor) was able to reverse (94,7±4,6% e 94,4±1,5% as compared to the control group, respectively) the antidepressant-like effect of mirtazapine (3 mg/kg, p.o.). Mirtazapine administered at a subeffective dose (0.3 mg/kg, p.o.) produced a synergistic antidepressant-like effect with methylene blue (20 mg/kg, i.p., direct inhibitor of both nitric oxide synthase and soluble guanylate cyclase), 7-nitroindazole (50 mg/kg, i.p., a specific neuronal nitric oxide synthase inhibitor) or ODQ (30 pmol/site, a specific inhibitor of soluble guanylate cyclase), (73,9±8,6%, 77,0±5,9% e 75,8±6,1% as compared to the control group, respectively). **Discussion:** Mirtazapine produced an antidepressant-like effect after p.o. administration in the FST in mice, at doses that did not affect locomotor activity. Moreover, the results indicate the involvement of the L-arginine-nitric oxide-cGMP pathway in the action antidepressant of mirtazapine in the FST, suggesting that an inhibition of nitric oxide and cGMP synthesis is implicated in the mechanism of action of mirtazapine. **Financial support: CNPq, CAPES, FINEP**

03.015

Involvement of the L-arginine-nitric oxide-CGMP pathway in the antidepressant-like effect of escitalopram in the forced swimming test. Zomkowski ADE, Engel D, Gabilan NH, Rodrigues ALS UFSC - Bioquímica

Introduction: Depression is a disorder that affects up to 20% of the population (Berton and Nestler, *Nature Rev. Neurosci*. 7: 137, 2006). Escitalopram is a specific serotonin reuptake inhibitor used in the treatment of depression and anxiety disorders (Burke et al., J. Clin. Psychiatry 63: 336, 2002). The present study was aimed at investigating the effect of escitalopram administered by oral (p.o.) route in the forced swimming test (FST) in mice. In addition, the involvement of the L-arginine-nitric oxide-cGMP in the antidepressant-like effect of escitalopram in the FST was investigated. **Methods:** Female Swiss mice (30-40 g, n=6/group) were used**.** The experiments were performed after approval of the protocol by the Institutional Ethics Committee (PP185). The FST was carried out in mice individually forced to swim in an open cylindrical container (diameter 10 cm, height 25 cm), containing 19 cm of water at 25 1C. The immobility time in a 6-min session in the FST was registered. Escitalopram was administered by p.o. route (0,1; 0,3; 1; 3 e 10 mg/kg), 60 min before the FST. In order to rule out non-specific locomotor activity, mice were submitted to the open-field test. Comparisons between treatment groups and control were performed by ANOVA followed by Tukey's HSD test when appropriate. A value of $P<0.05$ was considered to be significant. **Results:** The administration of escitalopram at doses of 0.1, 1, 3 e 10 mg/kg, p.o. significantly reduced (74,6±3,4%, 69,7±3,3%, 48,3±2,4% e 55,7±3,7%), respectively, the immobility time in the FST as compared to the control group (100%). These doses of escitalopram did not produce any change in ambulation in mice in an open-filed. The pre-treatment of mice with L-arginine (750 mg/kg i.p., a nitric oxide precursor) or sildenafil (5 mg/kg, i.p., a phosphodiestease 5 inhibitor) was able to reverse (79,3±3,3% e 94,6±3,7% as compared to the control group, respectively) the antidepressant-like effect of escitalopram (3 mg/kg, p.o.). Escitalopram administered at a subeffective dose (0.1 mg/kg, p.o., administered 30 min before) produced a synergistic antidepressant-like effect with methylene blue (20 mg/kg, i.p., a direct inhibitor of both nitric oxide synthase and soluble guanylate cyclase), 7-nitroindazole (50 mg/kg, i.p., a specific neuronal nitric oxide synthase inhibitor) or ODQ (30 pmol/site, a specific inhibitor of soluble guanylate cyclase), (63,7±6,8%, 81,6±4,9% e 69,9±6,7% as compared to the control group, respectively). **Discussion:** Escitalopram produced an antidepressant-like effect after p.o. administration in the FST in mice, at doses that were without effect on locomotor activity. The results indicate that the mechanism underlying the antidepressant-like effect of escitalopram involves an inhibition of either nitric oxide or cGMP synthesis, since its anti-immobility effect in the FST was reversed by a precursor of nitric oxide synthesis and a phosphodiesterase 5 inhibitor that increases cGMP levels, but potentiated by nitric oxide and cGMP inhibitors. Our results are in accordance with studies that have shown that nitric oxide synthase inhibitors exert antidepressant-like effects (Harkin et al, *Neuropharmacol*. 44:616, 2003). **Financial support:** CNPq, CAPES, FINEP

03.016

Comparison among neuroleptic generations in inhibiting spontaneous and cocaine induced locomotor activity in mice. Hollais AW[1], Melo CM[1], Baldaia MA[1], Santo, R[1], Talhati F[1], Araujo BA[1], Wuo-Silva R[2], Marinho EAV[1], Oliveira-Lima AJ[1], Frussa-Filho R[2]
[1]UBC/UNIFESP - Farmacologia, [2]UNIFESP - Farmacologia

Introduction: all drugs of abuse increase dopamine levels in the nucleus accumbens. In rodents such an increase produces locomotor stimulation that is sensitized after repeated drug administration. Within this context, locomotor sensitization has been proposed to share neuronal mechanisms with drug craving (Pierce, C.; Kumaresan, V. *Neurosc.and Biobehav*. Rev. 30, p.215, 2006). The aim of the present study was to compare neuroleptics haloperidol, ziprasidone and aripiprazole in their effectiveness to inhibit spontaneous locomotor activity (SL), cocaine-induced hyperlocomotion (CL) and cocaine-induced locomotor sensitization (CLS). **Methods:** three experiments were performed. In the first one, female swiss mice received an i.p. injection of saline (SAL), 0.01, 0.05, 0.10, 0.25, or 0.5 mg/kg haloperidol (H) and 30 min later were observed for 10 min in the open-field for locomotor activity quantification. Immediately after, animals were removed from the open-field, received a further i.p. saline or 10mg/kg cocaine (COC) injection and 5 minutes later were further observed for 10 min in the open-field for locomotor activity quantification. Seven days later all animals received an i.p. challenge injection of saline or 10 mg/kg cocaine and were observed for 10 min for open-field locomotion quantification. Thus, the groups were as follows: SAL-SAL-SAL, SAL-SAL-COC, SAL-COC-COC, H 0.01-COC-COC, H 0.05-COC-COC, H 0.1-COC-COC, H 0.25-COC-COC and H 0.5-COC-COC. In the second and third experiments, the same experimental design was performed except that ziprasidone (0.1, 0.5, 1.0, 2.5 and 5.0 mg/kg i.p.) or aripiprazole (0.1, 0.5, 1.0, 2.5 and 5.0 mg/kg) were used instead of haloperidol. **Results and Discussion:** ANOVA followed by Duncan's test revealed that haloperidol decreased SL and CL at the same dose range (0.1-0.5 mg/kg), and prevented CLS at the doses of 0.1 and 0.25 mg/kg only. Indeed, the SL presented by the H 0.1 group (64±9), the H 0.25 group (54±8) and the H 0.5 group (37±7) were significantly lower than the SL of the Sal group (106±15). Concerning haloperidol effects on CL, the H 0.1-COC group (35±5), the H 0.25- COC group (12±1) and the H 0.5-COC group (11±3) presented CL significantly lower than that presented by the SAL-COC group (64±9). As for CLS, its development was demonstrated by a significant increase of the locomotor activity of the group SAL-COC-COC (239±22) compared to the locomotor activity of the SAL-SAL-COC group (139±27). As mentioned above CLS was significantly prevented only in the H 0.1-COC-COC (138±27) and the H 0.25-COC-COC groups (136±11). Ziprasidone also decreased SL and CL at the same dose range (1.0-5.0mg/kg) but prevented CLS at lower doses (0.1-2.5 mg/kg). Aripiprazole decreased CL at lower doses (0.1-5.0 mg/kg) when compared to the doses that were effective in inhibiting SL (1.0-5.0 mg/kg). An also low dose range of aripiprazole was effective in preventing CLS (0.1-2.5 mg/kg). Interestingly, the higher dose of the three neuroleptics studied did not prevent CLS in spite of inhibiting SL and CL. Our results suggest that the second generation neuroleptic ziprasidone and mainly the third generation neuroleptic aripiprazole have higher efficacy in counteracting cocaine-behavioral effects when compared to the classical neuroleptic haloperidol.
Financial support: CNPq. CEP-0345/07

03.017

Lipoxin A_4: a new player on endocannabinoid neurotransmission suggests endogenous allosteric modulation of CB1 receptors. Pamplona FA[1], Ferreira J[2], Menezes de Lima Jr O[1], Calixto JB[1], Takahashi R[1] [1]UFSC - Farmacologia, [2]UFSM - Química

Introduction: Lipoxins and endocannabinoids are endogenous eicosanoids that are released on demand following neuronal stimulation or injury. Lipoxin-A_4 (LXA_4) activates ALX receptors and have important role in the resolution of peripheral inflammations, but information about its effects in the central nervous system are scarce. Endocannabinoids, such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG) exert widespread brain effects by activation of CB_1 cannabinoid receptors. Although both classes of compounds share structural and functional similarities, the pharmacological relationship between them was not yet described. Hence, our objective was to investigate the participation of the endocannabinoid system in the central effects of LXA_4 in mice. **Methods:** Swiss albino mice were injected i.c.v. with LXA_4 (0.01-1 pmol / 5μl) or control (ethanol 0.7%) and 5 min after evaluated in the mouse tetrad test (catalepsy, locomotion, analgesia and rectal temperature), considered predictive for cannabimimetic activity. These responses were further investigated injecting the CB_1 receptors antagonist rimonabant (1 mg/kg, i.p.) or the ALX receptors antagonist BOC-2 (10 μg/kg, i.p.) 50 min before i.c.v. injection of LXA_4 (1 pmol / 5 μl). The role of CB1 receptors on LXA_4 effects was confirmed by the use of CB_1 knockout mice. The pharmacological interaction between LXA_4 and the endocannabinoids was addressed by co-injecting sub-effective doses of AEA (10 pmol/ 2 μl) or 2-AG (1 pmol/ 2 μl) and LXA_4 (0.01 pmol/ 2 μl). Endogenous resting levels of LXA_4 in the brain were assessed by ELISA. Binding of LXA_4 (1nM - 10μM) at the CB_1 receptors was tested in a competitive binding assay against [^{3}H]rimonabant in mouse brain membranes (P2). The experimental protocols were approved and follow international guidelines on the ethic use of laboratory animals (CEUA-UFSC PP00280). **Results:** LXA_4 (0.1-1 pmol) induced catalepsy, hypolocomotion, analgesia and hypothermia in mice. These effects were antagonized by the CB_1 receptors antagonist rimonabant, but not by the ALX receptors antagonist BOC-2, and were absent in CB_1 knockout mice. LXA_4 potentiated the cataleptic effects of AEA, but not of 2-AG. Endogenous levels of LXA_4 in the brain were in the range of 2-10 ng/g of wet tissue, depending on the region. LXA_4 partially inhibit the binding of [^{3}H]rimonabant (Ki>10 μM), but pilot studies suggested that LXA4 (100nM) enhanced the AEA-induced (1 μM) inhibition of [^{3}H]rimonabant binding. There was no effect of LXA_4 on AEA-degrading enzyme FAAH activity (Ki>10 μM). **Discussion**: The present results suggest that LXA_4 exerts central effects via CB_1 cannabinoid receptors and interact positively with the endocannabinoid AEA. While we did not find any effect of LXA_4 on endocannabinoid metabolism, there is evidence that LXA_4 may potentiate AEA binding at CB_1 receptors through a mechanism of positive allosteric modulation. This is a pioneer finding on the endocannabinoid system pharmacology. **Acknowledgements:** CNPQ-Brazil, CAPES-Brazil. We are thankful to Dr. Filipe S. Duarte, for excellent technical contribution during the initial phases of the study. The CB1 knockout mice were kindly provided by Dr. Carsten T. Wotjak.

03.018

Antidepressant-like effect of the ethanolic extract from *Tabebuia avellanedae* in mice: possible evidence of the involvement of the monoaminergic system. Freitas AE[1], Lobato KR[1], Budni J[1], Machado DG[1], Binfaré RW[1], Jacinto J[1], Veronezi PO[2], Pizzolatti MG[2], Rodrigues ALS[1] [1]UFSC - Bioquímica, [2]UFSC - Química

Introduction: *Tabebuia avellanedae* (Bignoneaceae) is native to tropical rain forests throughout Central and South America commonly known as "pau-d´arco" and “ipê-roxo” in Brazil. Its inner bark is used as analgesic, anti-inflammatory, antineoplasic and diuretic in traditional folk medicine (Byeon et al., J Ethnopharmacol.119:145, 2008). Antinociceptive, antiedematogenic and antiulcerogenic properties have also been reported to this plant (De Miranda et al., BMC Pharmacol.1:6, 2001; Twardowschy et al., J Ethnopharmacol. 118:455, 2008). Considering that; a) pain and depression are often linked; b) several studies have indicated that pain and depression share common neurochemical mechanisms (Micó et al., Trends Pharmacol. Sci. 27:348, 2006); c) *T. avellanedae* is extensively used as analgesic in Brazil, the effect of the ethanolic extract of this plant was investigated in two behavioral models commonly used to detect antidepressant activity: forced swimming test (FST) and tail suspension test (TST) in mice. Moreover, the involvement of the monoaminergic system in the antidepressant-like effect of the extract in the TST was studied. **Methods:** The ethanolic extract from *T. avellanedae* or vehicle was administered by oral route (p.o.) in Swiss mice, 60 min before the FST, TST or open-field test. The immobility time in the FST, TST and the number of crossings in open- field paradigm were registered in a 6-min session. The procedures of this study were approved by the Ethics Committee of the Institution (pp00051/ceua). **Results and Discussion:** The results indicate that the extract of the *T. avellanedae* produces an antidepressant-like effect, since it significantly reduced the immobility time in the FST (100 mg/kg; 37.91 ± 1.62 %) and TST (10, 30 and 100 mg/kg; 20.04 ± 3.71%, 29.58 ± 5.32%, and 25.00 ± 4.65%) as compared to the control group=100%, respectively, without accompanying changes in ambulation in the open-field test. The anti-immobility effect of the extract (30 mg/kg, p.o.) in the TST, was prevented by pretreatment of mice with WAY100635 (0.1 mg/kg, s.c.., 5-HT_{1A} receptor antagonist; 88.31 ± 5.75%), ketanserin (5 mg/kg, i.p., a 5-$HT_{2A/2C}$ receptor antagonist; 110.60 ± 5.83%), prazosin (1 mg/kg, i.p., an α_1-adrenoceptor antagonist; 96.53 ± 4.34%), yohimbine (1 mg/kg, i.p., an α_2-adrenoceptor antagonist; 92.83 ± 1.34%), SCH23390 (0.05 mg/kg, s.c., a dopamine D_1 receptor antagonist; 97.85 ± 5.06%) or sulpiride (50 mg/kg, i.p., a dopamine D_2 receptor antagonist; 104.37 ± 6.25%). These results suggest that the antidepressant-like effect of the extract from *T. avellanedae* is mediated through an activation of the monoaminergic system. **Financial support:** FAPESC-SC, CAPES, CNPq, UFSC, FINEP-IBN-Net (01.06.0842-00).

03.019

SIN-1, a nitric oxide donor, increases locomotor activity when injected into the dorsal raphe nucleus of rats. Gatti RF, Souza LBG, Martins GG, Cardoso BM, Oliveira RMW
DFF-UEM

Introduction: The dorsal raphe nucleus (DRN) has been considered an important component of the brain circuit that mediates anxiety- and depression-related behaviors (Abrams et al., Ann. NY Acad. Sci.1018:46-57, 2004). It contains a large proportion of nitric oxide (NO)-producing neurons (Onstott et al., Brain Res. 610:317-324, 1993). Recently, it was demonstrated that direct injection of L-Arginine, a NO precursor into the DRN, resulted in an anxiolytic-like effect. This effect, however, was limited and the dose-response curve presented an inverted U shape. Otherwise, the NO synthase (NOS) inhibitor L-NAME into the DRN decreased the general motor activity of the animals, measured in the elevated plus maze model of anxiety (Spiacci et al., 2008; *Pharmacol. Bioch. Behav*. 88:247–255, 2008). Thus, NO may influence motor- and anxiety- related behaviors in the DRN. **Objective:** The aim of this study was to evaluate the locomotor effects produced by direct administration of the NO donor SIN-1 into the DRN of rats submitted to the open field model. **Methods:** Male Wistar rats (280-310 g) with stainless steel cannulae aimed at the DRN received microinjections of the saline or SIN-1 150 and SIN-1 300 nmol and, 10 min later, were submitted to the open field model for 10 min. The behavior was videotaped and the moved distance (cm) was calculated for each animal with the aim of Ethovision software. Data (mean±SEM) were analyzed by one-way analysis of variance (ANOVA) followed by the Tukey test for multiple comparisons. The experimental procedures were approved by the Ethics Committee on Animal Experimentation of the State University of Maringá, (CEEA n^{o} 003/2008). **Results and Discussion:** SIN-1 150 and 300 nmols into the DRN increased significantly the total moved distance when compared to control group ($F_{2,29}$=10.84, $p<0.001$; saline=3377±267.6; SIN-1 150 nmol=4685±328.7; SIN-1 300 nmol=6879±1119). The results confirm that NO influences motor- related behaviors in the DRN. However, further studies using NO scavengers, for example, are needed to elucidate the mechanism involved in these effects and to address the question if it can produce anxiolytic-like effects independently of motor effects.

03.020

Evaluation of piracetam effects on aversive memory using the rat elevated plus-maze trial 1/trial 2 protocol. Gazarini L[1], Oliveira RMW[2], Bertoglio LJ[1] [1]UFSC - Farmacologia, [2]DFF-UEM

Introduction: It has been shown that prior elevated plus-maze (EPM) test experience (trial 1) changes the behavioral pattern observed on the next exposure (trial 2) [1]. One of the hypotheses proposed to explain the augment in anxiety-related behaviors found in EPM-experienced rats is the retrieval of an aversive memory acquired throughout the trial 1 [2]. Based on this assumption, one could expect a further increase of them in rats on trial 2 if the acquisition and/or the consolidation of this aversive memory were improved. The objective of the present study was to investigate whether the systemic treatment with piracetam, a nootropic drug thought to facilitate the learning and memory processes, prior to or immediately after the EPM trial 1 would interfere with inhibitory avoidance and/or risk assessment behaviors displayed by rats already experienced in the EPM on trial 2. **Methods**: Male Wistar rats (300-350 g) were intraperitoneally administered with vehicle (NaCl 0.9 %) or piracetam (50, 100 or 200 mg/kg) 30 min before or immediately after the first EPM exposure. On the next day all groups were re-exposed to the EPM, undrugged. Behavioral measures scored during 5 min in both trial 1 and trial 2 were the percentage of open-arms time (%OAT), the percentage of open-arms entries (%OAE), stretched-attend postures (SAPs) and enclosed-arms entries (EAE). The experimental design aforementioned was approved by the local Ethical Committee in Animal Research (022-2007/CEEA/PPG/UEM). **Results:** Repeated-measures analysis of variance followed by Newman-Keuls test ($p<0.05$) showed an increase in SAPs during the trial 2 of EPM-experienced rats administered with piracetam either pre-trial 1 [$F(3,50)= 9.1$, $p<0.0001$; vehicle (mean ± S.E.M) = 10.1 ± 1.0, piracetam 100 mg/kg = 15.7 ± 0.8 and piracetam 200 mg/kg = 18.5 ± 1.6] or post-trial 1 [$F(3,56)= 6.0$, $p<0.001$; vehicle (mean ± S.E.M) = 7.2 ± 0.6 and piracetam 100 mg/kg = 11.8 ± 0.8]. No statistically significant differences were observed for %OAT, %OAE and EAE in piracetam-treated rats relative to controls during the trial 2. **Discussion:** EPM-experienced rats treated with piracetam prior to or immediately after trial 1 displayed more SAPs than controls on trial 2. The present results suggest that risk assessment behavior was intensified as a result of an improvement of aversive memory acquisition and/or consolidation. [1] Carobrez, A.P. et al. *Neurosci. Biobehav. Rev*. 29(8), 1193, 2005. [2] Stern, C.A. et al. Pharmacol. *Biochem. Behav*. 90(4), 545, 2008. **Financial support:** UEM, CNPq, CAPES, FAPESC and FAPESP.

03.021

Pindolol potentiates the panicolytic effect of paroxetine in the elevated t-maze. Sela VR[1], Roncon CM[1], Zangrossi Jr H[2], Graeff FG[3], Audi EA[1] [1]UEM - Farmácia e Farmacologia, [2]FMRP-USP - Farmacologia, [3]FMRP-USP - Neurociências e Ciências do Comportamento

Introduction: The β-adrenergic and 5-$HT_{1A/1B}$ receptor antagonist pindolol (PIN) has been used in combination with selective inhibitors of serotonin reuptake (SSRIs), to shorten the time of onset of clinical action and/or increase the proportion of the responders [1;2]. The aim of this study was to examine the interaction between PIN and the SSRI, paroxetine (PAR) using oral or intraperitoneal (i.p.) routes of acute administration, in rats tested in the elevated T-maze (ETM) model of generalized anxiety and panic disorders [3]. **Methods:** Male Wistar rats (230–250g; n= 6-13; UEM Ethics Committee 041/2004) were treated with either PIN (1.0; 5.0 or 15.0 mg/kg, i.p.), PAR (0.5; 1.5 or 3.0 mg/kg, i.p.) or vehicle (2% tween 80 saline, i.p). After 90 min from the injection, the animals were tested to the ETM. For assessing the drug combination effect, rats were treated at a 20-min interval with PIN (5.0 mg/kg, i.p.) and PAR (1.5mg/kg, i.p.) or with PIN (5.0 mg/kg, oral) and PAR (3.0 mg/kg, oral). As control (C), animals were treated twice with vehicle solutions. After 90 min from the last injection, the rats were tested to the ETM. Inhibitory avoidance and one-way escape were measured recording the latencies (s) to withdraw from the enclosed arm and to withdraw from the end of one of the open arms, respectively, in three consecutive trials. Repeated-measures ANOVA was used to analyze the data. When appropriate, one-way ANOVA was applied, followed by Duncan's multiple-range test. **Results and Discussion:** PIN 15.0 mg/kg (i.p.) increased both inhibitory avoidance latency ($p<0.05$) [baseline-C=21.3±25.7; PIN=152.5±27.2, avoid1-C=28.9±32.6; PIN=193.9±34.6, avoid2–C=64.5±35.4; PIN=263.2±37.6] and escape latency [escape3-C=10.3±3.3; PIN=24.7±3.5] in the ETM, probably due to nonspecific motor deficit [C=20.8±1.0; PIN=15.2±1.1]. PAR (3.0 mg/kg, i.p.) selectively impaired escape [escape3-C=6.2±4.7; PAR=20.6±4.0], ($p<0.05$) considered a panicolytic effect. Combination of PIN (5.0 mg/kg, i.p.) with an ineffective dose of PAR (1.5 mg/kg, i.p.) impaired escape [escape3-C=12.5±4.4; PIN+PAR=29.9±4.9], ($p<0.05$) indicating drug potentiation. By the oral route, neither PAR (3.0 mg/kg) nor PIN (5.0 mg/kg) alone were effective, but the combination of these same doses had a marked panicolytic effect [escape1-C=10.0±1.8; PIN+PAR=16.9±2.1, escape2-C=8.1±2.1; PIN+PAR=17.5±2.6, escape3-C=9.0±2.5; PIN+PAR=19.9±3.0], ($p<0.05$) indicating drug potentiation. With the exception of 15 mg/kg of PIN, i.p., the treatments did not modify the distance traveled by rats in the arena. The presently evidenced potentiation of the panicolytic effect of PAR by PIN fulfill the prediction from the hypothesis that blockade of 5-HT_{1A} autoreceptors would enhance the action of PAR. They also give preclinical support for the use of this drug combination in the treatment of PD. **References:** 1. Brousse G. *Encephale 29*: 338, 2003. 2. Hirschmann S. J *Clin Psychopharmacol 20*: 556, 2000. 3. Graeff FG. *Neurosci Biobehav* Rev *23*: 237, 1998. **Apoio finaceiro:** Capes/CNPq/ FAEPA

03.022

Acquisition and expression of olfactory fear conditioning following chemical stimulation of dorsolateral periaqueductal gray matter: effects of midazolam. Kincheski GC, Carobrez AP UFSC - Farmacologia

Purpose: Odor perception retrieves memories of life events with personal meaning and elicits strong affective experiences. Clinicians noted that specific trauma-associated odors such as, diesel fuel in combat veterans, can precipitate signs of pos-traumatic stress. Dangerous olfactory cues are able to activate neural structures related to defensive behavior (DB) including the dorsolateral part of the periaqueductal gray matter (dlPAG). The chemical stimulation of dlPAG in rats evokes DB as the result of internal mood alterations, typically found in aversive situations. The aim of present study was to test the hypothesis that the fear-like state induced by the chemical stimulation of dlPAG could be used as an unconditioned stimulus (US) generating olfactory fear conditioning (OFC) in previously neutral odor. In addition, the aversive nature of the OFC was evaluated in rats treated with midazolam (MDZ). **Methods:** Experimental procedure consisted of 2 phases: acquisition and expression of OFC. The acquisition phase consisted of 2 sessions: familiarization (5 min) and conditioning (10 min, 24 h after), where amyl acetate odor (AMYL) and the dlPAG microinjection were associated. The expression phase consisted of 2 consecutive sessions (10 min each): familiarization and test, performed in an odor box comprising an open and an enclosed communicating compartment. During the expression phase the DB was represented by: %time approaching the AMYL source (%AT) and %time hiding in the enclosed compartment (%HT). Male *Wistar* rats were conditioned after receiving (0.2µl) NMDA (100 pmol) or PBS into dlPAG. A second control group received NMDA into the dlPAG but was not exposed to AMYL. To evaluate the aversive nature of the OFC, rats received saline (SAL) or MDZ (0.5 or 1 mg/kg, IP) 30 min before the conditioning or 30 min before the test session. The protocols were approved according to the Animal Ethics Committee (23080.0055752/2006-64/UFSC). **Results:** ANOVA followed by Duncan revealed that rats conditioned with NMDA in the dlPAG significantly ($p<0.05$) increased the DB during the test, spending less time approaching the AMYL (%AT= 13±1), and more time hiding (%HT= 75±2) than the PBS group (%AT=25±4; %HT=52±8). In the second experiment, MDZ at the highest dose (1mg/kg) infused before OFC reduced the DB in the test session [MDZ: (%AT=38±6; %HT= 34±6); SAL :(%AT=15±4; %HT=71±5)]. MDZ infused at a lower dose (0.5 mg/kg), before the test session decreased the DB in the test session [MDZ: (%AT=40±5; %HT= 37±6); SAL (%AT=17±2; %HT=65±2)]. **Conclusions:** The results showed that dlPAG activation may be used as an interoceptive US, capable of conditioning previously neutral odor. In addition, MDZ impaired the OFC acquisition and the DB expression, emphasizing the pharmacological validation of this model in predicting putative anxiolytic drugs. Taken together, the results suggest the involvement of dlPAG in fear learning associations beyond its well known participation in the expression of DB. **Financial Support:** CAPES, CNPq, FAPESP, FAPESC.

03.023

Anxiolytic and panicolytic effect of the semi-purified fraction of guaraná [*Paullinia cupana* H.B.K. var. *sorbilis* (Mart.) Ducke]: involvement of serotoninergic neurotransmission. Roncon CM, Almeida, CB, Audi EA UEM - Farmácia e Farmacologia

Introduction: Guaraná (*Paullinia cupana* H.B.K. var. *sorbilis* (Mart.) Ducke) is used worldwide as a stimulant of the CNS. The raw extract, a semi-purified fraction (EPA) of guaraná and imipramine showed an antidepressant effect in rats submitted to the forced-swim test (patent applied for by the *Universidade Estadual de Maringá* no. 2747/00) [1]. Caffeine did not reproduced this result, suggesting that this effect was not due to the xanthine constituints. The objective of this study was to evaluate the effect of the semi-purified fraction (EPA) on rats submitted to the elevated T-maze test (ETM) [2]. We also assessed the involvement of serotoninergic neurotransmission in the effects of the EPA in the ETM, by means of association with metergoline, a non-selective antagonist of types 1A and 2A (5-$HT_{1A/2A}$) serotonin receptors. Locomotor activity was evaluated in a circular arena. **Methods:** Male Wistar rats (230-310 g; n=9-15; UEM Ethics Committee protocol 053/2008) were treated for 24 days by gavage with the vehicle (saline containing 2% tween 80), EPA (4, 8, and 16 mg/kg), or paroxetine (3 mg/kg, positive control) and submitted to the ETM for evaluation of the latency of inhibitory avoidance, related to generalized anxiety, and one-way escape, related to panic. Metergoline (3 mg/kg, i.p.) was administered five minutes before the EPA (8 mg/kg), paroxetine (3 mg/kg), or the vehicle. 60 min following the last administration, the animals were submitted to behavioral tests. Repeated-measures ANOVA was used to analyze the data. When appropriate, one-way ANOVA was applied, followed by Duncan's multiple-range test. **Results and Discussion:** EPA (8 and 16 mg/kg) and paroxetine (3 mg/kg) increased the escape latency, indicating a panicolytic effect compared to the control [escape 2–C=9.16±1.48; PAR=15.55±1.40; EPA= 8 mg/kg=15.0±2.10 ($p<0.01$)]. Paroxetine (3 mg/kg), EPA (8 mg/kg), and metergoline (3 mg/kg) associated with the vehicle increased the escape latency [escape 1-C=10.15±2.29; MET+VEI=22.11±2.76 ($p<0.01$), escape 2- C=8.23±3.44; PAR=20.46±3.44; EPA=20.23±3.44; MET+VEI= 22.55±4.13 ($p<0.05$), escape 3-C = 8.38±3.62; MET+VEI = 30.88;4.35 ($p<0.01$)]. The association of metergoline (3 mg/kg) with paroxetine (3 mg/kg) or EPA (8 mg/kg) blocked the increase in escape latency produced by each of the compounds [escape 1- C=10.15±2.29; MET+VEI=22.11±2.76 ($p<0.01$), escape 2–C=8.23±3.44; PAR+VEI = 20.46±3.44; EPA+VEI=20.23±3.44; MET+VEI=22.55±4.13; MET+PAR=7.88±4.13; MET+EPA=16.22±4.13 ($p<0.05$), escape 3-C=8.38±3.62; MET+VEI=30.88± 4.35 ($p<0.01$]. The distance run in the arena was not changed by the different treatments. The results show that the EPA produced a panicolytic effect in the ETM. The blockage of the panicolitic effect of EPA by metergoline shows that serotoninergic neurotransmission is involved in its mechanism of action. The other neurotransmission systems cannot be excluded. **References:** 1. Otobone. *Phytother Res 21*: 531, 2007. 2- Graeff FG. *Neurosci Biobehav R*ev *23*: 237, 1998. **Financial Support:** Capes

03.024

Efeito de extratos das partes aéreas de *Sonchus oleraceus* L. (serralha) sobre o sistema nervoso central em camundongos. Vilela FC, Giusti-Paiva A UNIFAL - Ciências Biomédicas

Introdução: A espécie *Sonchus oleraceus* é conhecida popularmente por possuir diversas atividades, e entre elas, age como "fortificante dos nervos", sugerindo um possível efeito sobre o SNC. Para verificar esta hipótese, avaliamos um possível efeito ansiolítico e antidepressivo dos extratos das partes aéreas de *Sonchus oleraceus* L em camundongos. **Métodos:** O material botânico seco, foi triturado e acondicionado em percolador com solução hidroetanólica 50% para obter o extrato hidroetanólico (EHSo) que foi seco em Spray Dryer. O mesmo material botânico foi também extraído com diclorometano por percolação para obtenção do extrato diclorometânico (EDSo). Os resíduos secos foram utilizados para investigar a atividade ansiolítica e antidepressiva em camundongos. Os animais (n = 10 animais por grupo) foram pré-tratados por via oral com veículo carboximetilcelulose 1% (10 mL/kg), extratos (30, 100 e 300 mg/kg), 0,5 mg/kg de clonazepam ou 10 mg/kg de amitriptilina 1 h antes de serem submetidos aos testes. O efeito ansiolítico de *S. oleraceus* foi avaliado em camundongos submetidos ao teste labirinto em cruz elevado e campo aberto. O efeito antidepressivo dos extratos foi avaliado no desempenho de camundongos no nado forçado e no teste de suspensão pela cauda que são modelos preditivos de fármacos antidepressivos. Os resultados foram analisados por ANOVA seguido pelo pós-teste de Newman-Keuls. Os protocolos experimentais foram aprovados pelo CEUA da Unifal-MG (200/2008). **Resultados e discussão:** No labirinto em cruz elevado, o EHSo e EDSo aumentaram a porcentagem de entradas de 15,2±3,3 % para 28,3±5,1 ($p<0,05$); 30,1±3,7 ($p<0,05$) e 34,2±2,9 % ($p<0,05$) nas doses de 30, 100 e 300 mg de EHSo e para 30,9±3,7 ($p<0,05$); 31,2±2,9 ($p<0,05$) e 48,8±5,7 % ($p<0,05$) nas doses de 30, 100 e 300 mg de EDSo. Os extratos também aumentaram o tempo nos braços abertos de 25,5±5,4 s para 70,2±6,2 e 86,1±18,2 s nas doses de 100 e 300 mg de EHSo; e para 63,8±13,6 e 84,0±16,1 s nas doses de 100 e 300 mg de EDSo. Os extratos induziram um efeito anti-tigmotático evidenciado por um aumento da atividade locomotora dos animais na parte central do campo aberto caracterizado pelo aumento da razão cruzamentos centrais/periféricos de 5,02±0,6 $x10^{-2}$ para 9,33±1,1 $x10^{-2}$ ($p<0,05$); 13,3±1,0 $x10^{-2}$ ($p<0,05$) e 15,6±1,3 $x10^{-2}$ ($p<0,05$) nas doses de 30, 100 e 300 mg de EHSo e para 11,9±1,2 $x10^{-2}$ ($p<0,05$); 21,3±2,7 $x10^{-2}$ ($p<0,05$) e 18,3±2,2 $x10^{-2}$ ($p<0,05$) nas doses de 30, 100 e 300 mg de EDSo. Os extratos administrados nas doses de 30-300 mg/kg, v.o. exerceram um efeito ansiolítico similar ao clonazepam. O tempo de imobilidade no teste de suspensão pela cauda foi reduzido ($p<0,05$) quando tratados com EHSo (125±15,9 e 137±4,9 s respectivamente nas doses de 100–300 mg/kg) ou com EDSo (141±14,6 e 83±12,1 s respectivamente nas doses de 100–300 mg/kg) quando comparado com o grupo controle (184±10,8 s) e semelhante ao efeito da amitriptilina (63,1±18,3 s). Da mesma forma, tempo de imobilidade no teste nado forçado foi reduzido ($p<0,05$) quando tratados com EHSo (44,1±2,7 e 40,0±3,8 s respectivamente nas doses de 100–300 mg/kg) ou com EDSo (40,7±5,6 e 33,6±3,5 s respectivamente nas doses de 100–300 mg/kg) quando comparado com o grupo controle (77,0±5,1 s) e semelhante ao efeito da amitriptilina (34,5±4,1 s). **Conclusão:** EHSo e EDSo induziram ao efeito ansiolítico, uma vez que os animais tratados com os extratos mostraram um aumento significante em ambas às porcentagens de entrada e tempo nos braços abertos do labirinto em cruz elevado. O aumento de locomoção dos animais no centro do campo aberto sugere um comportamento anti-tigmotáxico que pode ser interpretado como um efeito ansiolítico, semelhante ao clonazepam. Os extratos também indicaram um efeito antidepressivo, uma vez que reduziram o tempo de imobilidade no teste de suspensão pela cauda e nado forçado. **Apoio:** CAPES; FAPEMIG.

03.025

Role of context, shock intensity and duration to induce learned helplessness in rats.

Donadon, FM, Padovan CM - FFCLRP-USP - Psicologia e Educação

Introduction: Learned Helplessness (LH) is an animal model of depression which involves previous exposure to inescapable electric shocks (IS) that lead to an impairment in the performance in a subsequent exposure to signalized escapable shocks (ES). Data from the literature shows different protocols to induce LH that varies in intensity, duration and frequency of IS as well as the place where these shocks are delivered. Recently, great attention has been paid to ethical aspects involving animals in research, trying to minimize their suffering during research trials. Therefore, the aim of our work was to validate an LH protocol, using reduced intensities and duration of IS/ES presented to rats. All procedures were approved by the local Animal Ethics Committee (CEUA) of the USP Ribeirão Preto (protocol 06.1.1131.53.0) **Methods:** Male wistar rats (330g) were pre-exposed (PE) or not (NS) to 40 IS or ES, which varied in intensity and duration (seconds) in a shuttle box. 24 hrs later they were exposed to the same (sSB) or differentiated (dSB, walls coated with black bands) shuttle box, in which they received 30 ES signalized by a light stimulus that remained on until the end of the shock. Shocks could be avoided (during light presentation) or terminated by single crossing to the opposite side of the box. The groups (G) were: G1) IS(PE:0,6mA;5";sSB; T:0,4mA;5";n=12); G2) IS(PE:0,6mA;10";sSB; T:0,4 mA;10";n=3); G3) IS(PE:0,6 mA;10"; dSB; T:0,4mA;10"; n=6); G4) IS(PE:0,8 mA;10";sSB; T:0,6mA;10";n=4); G5) ES(PE:0,6mA;5";sSB; T:0,4mA;5";n=17); G6) ES(PE:0,6mA;10";sSB; T:0,4mA;10"; n=12); G7) ES(PE:0,6mA;10";dSB; T:0,4mA;10";n=6); G8) ES(PE:0,8mA;10";sSB; T:0,6mA;10";n=6); G9) NS(T:0,4mA;5";sSB;n=11); G10) NS(T:0,4mA;10";dSB;n=6); G11) NS(T:0,6mA;10";sSB;n=2). Latency (LAT) and number of failures (FAILURE) to avoid/escape shocks during test session were registered and analysed by repeated measures ANOVA (rmANOVA, $p<0.05$) followed by Duncan test. Data are represented as mean±SEM (standard error of the mean) for all LAT measured. Percent of LH (%LH) animals per group were calculated considering FAILURE>10 and analyzed by Chi-Square test. **Results:** rmANOVA indicated a significant difference between groups ($F_{12,80}=10.52$; $p<0.05$) being LAT greater in groups exposed to IS (G1:73±1; G2:100±0; G3:92±3; G4:98±2) and ES sSB(G5:67±2; G6:85±5; G8:89±6) when compared to NS (G9:59±2; G10:59±6; G11:64±2) and ES dSB(G7:58±10). IS (G1:92; G2:100; G3:100; G4:100) and CE sSB (G5:71; G6:75; G8:83) also increased %LH ($X=38,424$; $p<0,05$) when compared to NS (G9:27; G10:17; G11:0) and CE dSB(G7:17) groups. **Conclusion:** The context in which animals are pre-exposed to IS interferes on the behavioral consequences of this exposure. Moreover, combining a lower intensity of IS to different contexts for PE and test were able to induce LH, without impairing their performance when rats are pre-exposed to ES. Affiliation: SBFTE. Financial Support: CAPES, CNPq and FAPESP.

03.026

Central depressor activity of *Chondrodendon platyphyllum* total alkaloids fraction. Lima MRV[1], Montenegro FC[1], Sena MCP[1], Barbosa Filho JM[1], Almeida RN de[2], Araújo DAM[3] [1]UFPB - Tecnologia Farmacêutica, [2]LTF-UFPB - Fisiologia e Patologia, [3]UFPB - Biologia Molecular

Introduction: *Chondrodendron platyphyllum* is used in folk medicine at fever treatment caused by malaria and as antispasmodic (Tang, *Act. Pharm*., vol. 1, p. 17, 1978). Chondrodendon genus belongs to Menispermaceae family and it has been reported on literature that some species from this family exert activity on central nervous system (CNS) (Almeida, *J. of Ethnopharm*, vol. 243, p. 67, 1998; Almeida, *Phyto*, vol. 8, p. 340, 2001). The aim of present work was to evaluate the central depressor activity of total alkaloids fraction root bark (TAF) obtained from this specie. **Methods**: For all tests performed, we used adult male albino Swiss mice weighting 25-40 g. Animals were housed in appropriate cages and submitted to a 12/12-h light/dark cycle with free access to food and water. All animals were acclimatized before the experiments and all experimental observations were conducted between 12h00-17h00. Animals were killed by cervical dislocation and all procedures were carried out in accordance with Ethical Committee guidelines (CEPA/LTF-UFPB, process number 0206/08). All substances tested were injected by intraperitoneal route. In sleeping time induced pentobarbital-induced (PTB) animals were divided in two groups. Control group received a solution of distillated water plus 5% Tween and experimental received 200 mg/kg of TAF. After 30min of drug administration, animals received pentobarbital 40 mg/kg. Latency and sleeping time were recorded. In Formalin test, animals were divided in 5 groups: control, positive control and three experimental. Experimental groups received doses (100, 150 and 200 mg/kg) of TAF, control group received a solution of distillated water plus 5% Tween 80 and positive control received morphine 10 mg/kg. After 30min of drug administration, formalin 2.5% was injected on right hind paw and licking time of this paw was recorded for 30min (0-5min, 1st phase; 15-30min, 2nd phase). All experimental data obtained in sleeping time methodology were evaluated by Student's *t* test and in formalin test were evaluated using one-way analysis of variance (ANOVA) followed by Tukey's test. Differences were considered to be statistically significant when $p<0.05$. Data are expressed as mean ± error. **Results and Discussion:** Treatment with TAF 200 mg/kg didn't affect latency or sleeping time induced by PTB. Control group latency was 348.3 ± 115.3 s (n=8, $p>0.05$) and experimental was 570.5 ± 141.6 s (n=8, $p>0.05$). Sleeping time of control was 97.6 ± 17.6 min (n=8, $p>0.05$) and experimental was 82.3 ± 6.8 min (n=8, $p>0.05$). Formalin test treatment with TAF showed antinociceptive effect. First phase control group licking time was 94.3 ± 6.2 s (n=8, $p<0.05$), group treated with TAF 200mg/kg was 58.1 ± 9.6 s (n=8, $p<0.05$) and morphine treat animals were 19.0 ± 8.7 s (n=8, $p<0.001$). Second phase treatment with TAF 100 mg/kg reduced licking time when compared with control group from 214.1 ± 29.7 s to 120.6 ± 25.8 s (n=8, $p<0.01$); treatment with TAF 150mg/kg to 18.4 ± 11.8 s (n=8, $p<0.001$), treatment with TAF 200 mg/kg to 14.0 ± 13.6 s (n=8, $p<0.001$) and treatment with morphine 10 mg/kg to 5.2 ± 5.2 s (n=8, $p<0.001$). From these results we conclude that TAF of *C. platyphyllum* treatment showed antinociceptive effect. **Financial Support:** CAPES

03.027

Attenuation of the behavioral consequences of forced swim stress by blockade and activation of NMDA receptors in the median raphe nucleus of stressed rats before re-exposition. Pereira DHS, Padovan CM - FFCLRP-USP - Psicologia e Educação

Introduction: Exposure to uncontrollable stressors leads to behavioral and neurochemical changes, which has been associated to mal functioning of the Median Raphe Nucleus (MnRN)-Dorsal Hippocampus (DH) serotoninergic pathway. These deficits can be attenuated by intra-hippocampal injections of NMDA antagonists or 5-HT1a agonists. Activation of MnRN glutamatergic NMDA receptors (NMDAr) increases serotonin release in both MnRN and DH. We previously showed that MnRN injections of NMDA (NMDAr agonist) and/or AP7 (NMDAr antagonist) after pre-test and injection of AP7 before pre-test attenuated total time immobile in the forced swim test (FST). In this study we investigated whether activation of MnRN NMDAr before re-exposure to swim stress could prevent the effects of previous stressor. This project is approved by the Animal Ethics Committee of USP Ribeirão Preto (protocol 07.993.53.9). **Methods:** Rats with cannulas aimed to the MnRN were forced to swim for 15 min (Pre-Test) in an acrylic tank (55cm diameter, 22cm height, water temperature: 25°C). 24 hrs later they received two intracerebral injections (0.2µl each) of Saline (Sal), AP7 and/or NMDA (5 min interval), administered as follows: Sal+Sal (n=10), Sal+NMDA (1nmol; n=11), AP7+Sal (3nmols; n=10) and AP7+NMDA (n=13). Test was performed 5 minutes after the second injection. Latency to display immobility and total time immobile were registered. After test, all animals were sacrificed under deep anesthesia, perfused and had their brains removed for histological analysis to confirm site of injection. Only animals who had their sites of injection confirmed were used in the analysis (ONEWAY ANOVA/Tukey test). Numbers represent mean±standard error of mean in seconds (sec). **Results:** Treatment with AP7+Sal(204,6±27,9) and AP7+NMDA(237,6±17,1) increased latency to display immobility when compared to Sal+Sal(43,8±7,72) treated animals ($F_{3,43}$=25,06; $p<0.05$), while Sal+NMDA(78,6±18,4) group did not. For total time immobile, treatment with Sal+NMDA(61,3±10,6), AP7+Sal(23,7±8,3) and AP7+NMDA(14,2±6,1) significantly reduced immobility when compared to control group (Sal+Sal=128,4±11; $F_{3,43}$=32,58; $p<0.05$). **Conclusions:** Our data suggest that both activation and blockade of MnRN NMDAr glutamatergic neurotransmission in stressed rats facilitate the behavioral adaptation to an uncontrollable stressor. The mechanisms underlying such adaptation could be related to intrinsic mechanisms of the MnRN, involving release of serotonin within this structure and also in the hippocampus by indirect activation of interneurones or direct activation of this via, respectively, as supported by physiological studies. **Affiliation:** SBFTE. **Financial Support:** CNPq e FAPESP.

03.028

A role for NO in the anxiogenic effect induced by abstinence of chronic ethanol consumption. Padovan CM[1], Batistela, M. R.[1], Queiroz RHC[2], Tirapelli CR[3] [1]FFCLRP-USP - Psicologia e Educação, [2]FCFRP-USP - Toxicologia, [3]EERP-USP - Farmacologia

Introduction: Abstinence to chronic ethanol consumption (CEC) leads to anxiogenic effects. NO levels are increased in this condition and the Dorsal Raphe Nucleus (DRN) has increased levels of the NO synthesizing enzyme Nitric Oxide Synthase (NOS). Therefore, the aim of our work was to investigate whether intra-DRN administration of L-NAME (a non-specific NOS inhibitor) or 7-NI (nNOS inhibitor) attenuates the abstinence-induced anxiogenic-effect of CEC in rats. All the procedures were approved by the local Animal Ethics Committee (CEUA) of the USP Ribeirão Preto (protocol 07.1.992.53.2). **Methods:** Male wistar rats with cannulas aimed at the DRN received a 6%(v/v) ethanol(EtOH) or water (W) solution to drink for one (acute-AC) or 21 (chronic-CHR) days. After this, animals received only water for 48hrs until test in the elevated plus maze (EPM). Five min before test in the EPM, animals received an intra-NDR injection of L-NAME (100nmols/0.2µL, dissolved in sterile saline), 7-NI (10 nmols/0.2µL, in 15%DMSO), saline (SAL) or vehicle (Ve; DMSO 15% in sterile saline). Percentages of entries (%EO) and time spent (%TO) in the open arms were registered and analyzed by three-way ANOVA (effects of period of intake (TIME), ethanol (EtOHxW; DRINK) and intra-NDR treatment (DRUG), followed by Duncan test. Significance was set at $p<0.05$. Means±SEM are represented. **Results:** Abstinence of CEC decreased time spent in open arms (W: SAL=21.3±4.4;EtOH:SAL=6.5±2.3; effect of TIME:F1,152=2,82;p<0,05;and DRINK F1,152=6.50; p<0.05). Conversely, acute ethanol intake did not alter %TO (AC W:SAL=8.2±1.8;n=14;AC EtOH:SAL = 11.7±4.1; n=10). This effect was attenuated by intra-NDR administration of L-NAME (AC W:LNAME=12.9±4.6;AC EtOH:LNAME=8.9±2.0;CHR W:LNAME=14.3±3.6;CHR EthOH:LNAME=10.8±1.9), but not 7-NI (AC W:Ve=16.4±5.6;n=7;7NI=12.7±3.9;n=8;AC EtOH:Ve=10.7±2.8; n=9;7NI=11.1±2.4;n=9;CHR W:Ve=17.5±3.6;7NI=17.1±3.5;CHR EtOH:Ve=12.6±2.8;7NI=14.5±3.1). Administration of LNAME attenuated the abstinence-induced anxiogenic-effect of CEC on %EO (CHR W:SAL=35.7±3.2; LNAME=25.0±4.9;CHR EthOH:SAL=10.8±3.4;LNAME=28.5±3.8;Effects of TIME and DRINK (F1,152=4.88; p<0.05) and between DRINK and DRUG (F3,152=5.11; p<0.05)). No differences were seen after treatment with 7-NI (CHR W:Ve=29.5±1.6;7NI=29.5±3.2;CHR EthOH:Ve=21.3±3.1;7NI=23.9±3.9). No changes were observed after abstinence of acute ethanol consumption (AC W:SAL = 24.7±3.9; LNAME = 22.3±4.9;Ve=22.8±5.6;7NI=25.8±3.6;AC EtOH:SAL = 17.1±5.3; LNAME = 28.9±3.6;Ve=22.5±5.0;7NI=27.6±3.8). **Discussion:** CEC leads to anxiogenic effects detected in the EPM, which were attenuated by intra-DRN treatment with L-NAME, but not 7-NI. These results suggest that NO in involved in this response. However, NO generation does not seem to involve activation of nNOS. **Affiliation**: SBFTE. **Financial Support:** CAPES and FAPESP.

03.029

Chronic administration of medroxyprogesterone does not have an antimanic-like effect in the methylphenidate-induced hyperlocomotion model. Martynhak BJ[1], Pereira M[1], Correia D[1], Baretta IP[2], Andreatini R[1] [1]UFPR - Farmacologia, [2]UNIPAR - Ciências Biológicas, Médicas e da Saúde

Introduction: Recent studies have demonstrated that tamoxifen has antimanic-like effects in the amphetamine-induced hyperlocomotion model, which has been imputed to protein kinase C (PKC) inhibition. However, since tamoxifen also acts as estrogen receptor antagonist, we previously tested different doses of medroxyprogesterone (MPA), an antiestrogenic progestin without PKC activity, in acute tests and observed that MPA (3 mg/kg) partially blocked amphetamine-induced hyperlocomotor. Thus, the objective of this study was to evaluate the effects of chronic treatment with MPA (3 mg/kg) in Swiss mice. The study was approved by the Ethics Animal Experiment Committee of the Setor de Ciências Biológicas of Federal University of Paraná (certification number: 306). **Methods:** In order to validate the model, 29 male Swiss were divided into two groups: chronic (14 days) administration (i.p) of saline or lithium carbonate (Li, dissolved in saline and corrected to pH 7.0 using 2N HCl). Spontaneous locomotor activity was measured in rectangular chambers equipped with three photocells on the walls. The number of beam interruptions was cumulatively recorded. In test day, animals received Li or saline just before being placed into the individual chambers. After 30 minutes in the box, animals were given saline or methylphenidate (5mg/kg, dissolved in saline, s.c). Then, animals were kept in the chambers for additional 70 min and the number of beam interruptions were recorded each 10 min. To test the MPA effects, 24 male Swiss mice were divided into two groups: chronic (21 days) administration (s.c.) of saline or MPA (3mg/kg, dissolved in saline and tween). Before the test, animals received saline or MPA (s.c) and saline or methylphenidate (5mg/kg, s.c) after 30 minutes. Total ambulation after methylphenidate was also measured (cumulative beams interruptions during last 70 min). Data were analyzed by two-way ANOVA (both treatments as factors) followed by Duncan's post-hoc test when appropriated. Since the raw data did not fit into a normal distribution, logarithmic transformation was made. **Results:** A peak of hyperlocomotion was observed between 50 and 60 min after beginning of the test (20 and 30 min after methylphenidate). Lithium chronic administration blocked methylphenidate-induced hyperlocomotion, abolishing the peak of locomotor activity (50 and 60 minutes of test; $p<0.05$) and also reducing the total of beam interruptions [$p<0.05$; Li group: 637.0 ± 158.3 and saline group: 1115.3 ± 136.1 (mean ± standard error)]. There were no significant difference between MPA and saline after methylphenidate administration. **Conclusions:** Our results suggest that antiestrogenic drugs did not show antimanic-like effect in methylphenidate-induce hyperlocomotion model. Since this model showed good predictive validity (Li chronic treatment inhibited methylphedidate-induced hyperlocomotion), ours results reinforces the proposal that tamoxifen antimanic-like effects previous studies may be due only to PKC inhibition. **Financial Support:** CNPq

03.030

Papel do receptor 5HT2A na expressão do efeito ansiolítico e da sensibilização ao efeito estimulante do etanol em camundongos. Correia D, Iurk EK, Cabral RGC, Iaquinto YT, Bovo PFB, Lacerda A, Driessen B, Cretella ABM, Bona MPS, Boerngen-Lacerda R UFPR – Farmacologia

Introdução: O efeito ansiolítico do etanol atua como um reforçador negativo e estaria implicado na sua adição em decorrência da automedicação de transtornos psiquiátricos. O efeito estimulante do etanol é importante para sua propriedade reforçadora e o desenvolvimento de sensibilização para esse efeito após etanol crônico tem sido implicado com a adição. Há evidências da participação da serotonina em ambos efeitos, mas seu exato papel não está esclarecido. Neste trabalho avaliou-se o efeito de um desafio agudo com ketanserina, um antagonista específico do receptor 5HT2A, sobre a expressão do efeito ansiolítico e do efeito estimulante em animais tratados previamente com etanol crônico. **Métodos:** camundongos machos Swiss (Autorização do Comitê de Ética Animal do Setor de Ciências Biológicas da UFPR número 332) foram tratados por via i.p. diariamente com salina (S) ou etanol 2g/kg (E) sendo testados no 21^{o} dia no labirinto em cruz elevado durante 3 minutos, para quantificar o efeito ansiolítico do etanol através do parâmetro de porcentagem de tempo no braço aberto do labirinto, e na caixa de atividade durante 3 minutos para verificar o desenvolvimento de sensibilização ao efeito estimulante do etanol. Após 3 dias sem tratamento, visando verificar a expressão do efeito ansiolítico e da sensibilização, os animais foram desafiados com etanol na presença de ketanserina (K1-1,25 ou K2-5 mg/kg i.p.) e expostos novamente aos testes comportamentais (n=17 a 19/tratamento). Os dados foram analisados por ANOVA e teste de Newmann Keuls. **Resultados:** O efeito ansiolítico do etanol esteve presente em todas as avaliações, aguda S=20±3,0; E=47±4,9) e crônica (E=47±7,2). A ketanserina foi ansiogênica no teste desafio e bloqueou totalmente o efeito ansiolítico do etanol atingindo significância estatística na sua dose maior (K1+E=32±7,0; K2+E=19±7,9). O etanol crônico desenvolveu sensibilização comportamental ($E_{cronico}$=108±; E_{agudo}=114±13,3; S=78±9,6) e a sua expressão não foi observada no desafio com ketanserina (K1+E=22±6,0; K2+E=8,9±2,9). Notou-se também que a ketanserina sozinha, nas duas doses empregadas, causou efeito depressor da locomoção. **Conclusão:** Em estudos anteriores foi observado que a ketanserina associada ao etanol cronicamente preveniu a ansiogenese do reteste observada nos grupos controles (salina e somente ketanserina), ou seja, não interferiu no efeito ansiolítico do etanol quando este é administrado cronicamente. Porém, quando associada agudamente ao etanol foi capaz de bloquear a expressão do efeito ansiolítico. Isto sugere um papel importante do receptor 5HT2A principalmente no que se refere ao tratamento de transtornos pelo uso de álcool, pois o bloqueio desse receptor poderia ser útil na retirada do etanol. Também já havia sido observado que a ketanserina bloqueou o desenvolvimento de sensibilização para o efeito estimulante do etanol e no estudo atual, essa droga bloqueou também a sua expressão. A ativação dos receptores 5-HT2A aumenta a liberação de dopamina no núcleo *accumbens* (NAcc), sendo importante no efeito estimulante do etanol e no desenvolvimento de sensibilização comportamental. O bloqueio desses receptores diminuiria a liberação de dopamina no NAcc, impedindo a expressão da sensibilização ao efeito estimulante do etanol. Apoio financeiro: CAPES

03.031

Basal anxiety levels have no influence on ethanol intake in an addiction model in mice. Correia D[1], Ribeiro AF[2], Lopes C.[3], Bona MPB[3], de Lima LP[3], Cabral EGC[1], Cabral RGC[1], Eiras NO[3], Osaku LA[3], Godard ALB[3], Boerngen-Lacerda R[4] [1]UFPR - Farmacologia, [2]UFMG - Biologia Geral, [3]UFMG - Genética

Introduction: Alcohol dependence is associated with high rates of lifetime anxiety, which generally precedes the development of alcohol use disorders. It has been proposed that anxiety plays a role in the alcohol addiction development but the exact mechanisms remain unexplained. The present study aimed to verify the relationship between basal anxiety levels and ethanol intake in mice exposed to an addiction model validated in our laboratory previously. **Methods**: Drug-free Swiss mice (n=200) were exposed to the plus-maze test (PM), twice with 7 day-interval, and then, considering their percent open arm time (%OT) were characterized as high-anxiety (HA, n=37, %OT below the mean minus one standard deviation, i.e. 53.5 – 17.5 = 36%) and medium-anxiety (MA, n=96, %OT between mean ± one standard deviation, i.e. 36 to 71%). Then, HA and MA mice (n=29-30/group) were individually housed and exposed to a free-choice treatment for 10 weeks (acquisition phase – AC), during which they had free access to ethanol 10% and 5% (v/v), and water. Over the next 2 weeks, only tap water was provided (withdrawal phase – W). Approximately 5 hours after ethanol withdrawal, the animals were submitted to the PM in order to measure their anxiety indices. For the following 2 weeks, the ethanol solutions were again offered in a free choice schedule (re-exposure phase –RE). At the end of this period, the ethanol solutions were adulterated with 0.005 g/L quinine, creating an aversive bitter-tasting solution, and were offered to the animals for a further 2 week period (adulteration phase – AD). HA and MA control mice (n=8-10/group) had access only to water. All animal procedures were approved by the Ethics Committee for Animal Experimentation of the Setor de Ciências Biológicas, Universidade Federal do Paraná, certificated number 281. **Results:** Mice were characterized as: addicted (A - preference for ethanol without reducing intake when ethanol were adulterated with quinine); non-addicted heavy drinker (H - preference for ethanol but reduced ethanol intake when adulterated); and non-addicted light drinker (L - preference for water during all phases). No difference was observed between HA and MA regarding their ethanol intake pattern (for example for the AD phase: A-HA: 10.3±0.83; A-MA: 10.4±0.75; H-HA: 9.9±0.87; H-MA: 7.7±0.82; L-HA: 6.9±0.78; L-MA: 5.9±0.78). No correlation was observed between the ethanol intake in any phase and the percent open arm time (%OT) measured both in the basal tests (HA: r = -0.004; MA: r = 0.06) and during the W phase (HA: r = 0.39; MA: r = -0.0004). The differences in %OT between HA and MA groups persisted in the PM evaluation performed 5 hours after ethanol withdrawal, suggesting that they were characterized by a “trait” anxiety profile. **Conclusion:** The data suggest that high anxiety trait levels are not a determinant factor to high ethanol intake, at least in these experimental conditions. These results bring to light the discussion if: anxiety promotes alcoholism or alcoholism promotes anxiety disorders or the comorbid conditions are promoted by a shared third factor. **Financial support**: CNPq and CAPES.

03.032

Avaliação da atividade central de *Pera leandrii* (Euphorbiaceae) em camundongos.

Lima MRV[1], Sena MCP[1], Morais LCSL[1], Almeida RN de[2], Fonsêca DV[1], Salgado PRR[1]
[1]LTF-UFPB, [2]UFPB - Fisiologia e Patologia

Introdução: Os produtos naturais incluindo as plantas medicinais têm, ao longo da história, sido utilizados como fonte principal para a obtenção de novas drogas com potencial efeito terapêutico. Inúmeros avanços em psicofarmacologia têm sido obtidos através de estudos experimentais comportamentais, considerando-se o desenvolvimento de novas alternativas farmacológicas que possam ser utilizadas no tratamento da ansiedade, epilepsia e alívio da dor. Assim, o presente trabalho investigou possíveis efeitos psicofarmacológicos em modelos animais do extrato etanólico da *Pera leandrii* (EEPl), a fim de contribuir para o avanço do conhecimento científico sobre os efeitos terapêuticos da família Euphorbiaceae. **Métodos:** Camundongos *Swiss* (n=8) machos albinos (30-40g), foram tratados, via i.p., com: 500, 1000 e 2000 mg/kg de EEPl para realização de: 1) triagem farmacológica comportamental; Estabeleceu-se a dose de 500mg/kg para os testes subseqüentes com base nos resultados dessa: 2) teste de potencialização do tempo de sono induzido pelo pentobarbital; 3) teste do Rota Rod, observando-se a permanência dos animais na barra giratória, a uma velocidade constante de 7 r.p.m., por 3 min; 4) teste da formalina avaliando-se o tempo que o animal permanece lambendo a pata posterior direita, tratada com injeção de 20µL de formalina 2,5% na área subplantar dessa pata, durante os primeiros 5min (1ª fase) e de 15-30min (2ª fase) após administração de formalina na pata, tendo como grupo padrão morfina na dose de 6mg/kg. Estes procedimentos experimentais foram analisados pelo CEPA- Comitê de Ética em Pesquisa Animal do LTF/UFPB, sob a certidão nº 0307/08. **Resultados:** Os resultados foram analisados estatisticamente através do programa GraphPad Prism 4.00, empregando-se o teste t de Student não pareado para as metodologias 2 e 3, ANOVA seguido do teste de Dunett para o número 4, sendo tais resultados considerados significativos quando $p<0,05$. Os camundongos tratados com o EEPl (500 mg/kg) apresentaram diminuição da ambulação, analgesia e constipação na triagem farmacológica. A dose de 500 (60.6 ± 4.2 min) induziu aumento do tempo de sono dos animais quando comparados com o grupo controle (38.1 ± 5.8 min), não alterando a latência para início do sono (342.6 ± 67.9 s) quando comparados com o grupo controle (282.0 ± 20.1 s). O teste do Rota Rod não promoveu relaxamento muscular, incoordenação motora, ou neurotoxicidade por não ter alterado significativamente o tempo de permanência na barra giratória nos 30 (158,6 ± 16,2 s e 168 ± 12,0 s), 60 (157,6 ± 14,7 s e 179,4 ± 0,6 s), e 120 (150,1 ± 21,5 s e 179,0 ± 0,7 s) minutos após administração das substâncias, comparando a dose de EEPl 500 mg/kg ao grupo controle, respectivamente. No teste da formalina, EEPl (500 mg/kg) diminui o tempo de lambida da pata: 67,43 ± 3,0 s e 13,3 ± 6,3 s; na primeira e segunda fase do teste, respectivamente, em relação aos animais do grupo controle: 96,8 ± 11,2s e 254,6 ± 15,9 s. **Discussão:** EEPl apresenta efeitos psicofarmacológicos sugestivos de droga psicoléptica, com promissora atividade do tipo antinociceptiva que pode ser mediada tanto perifericamente como em nível central. **Apoio financeiro:** PIBIC/CNPq

03.033

Avaliação do efeito ansiolítico, antidepressivo e hipnótico de *Valeriana prionophylla* Standl. em modelos farmacológicos específicos. Holzmann I[1], Cechinel Filho V[2], Cruz S M[3], Martínez JV[4], Santizo A[3], Caceres A[3], Souza MM[5] [1]UNIVALI - Farmácia, [2]NIQFAR-UNIVALI - Ciências Farmacêuticas, [3]Universidad de San Carlos - Ciencias Químicas y Farmacia, [4]Universidad de San Carlos - Agronomía, [5]UNIVALI - Ciências da Saúde

Introdução: A espécie *Valeriana prionophylla* Standl. pertence à família Valerianaceae, conhecida no Brasil como "sonífera" e na Guatemala como "Valeriana de monte", onde tem sido bastante utilizada na medicina popular como calmante, sedativa, hipnótica e ansiolítica. O objetivo do presente estudo foi investigar os efeitos do extrato hidroalcóolico seco (EH) obtido dos rizomas da planta coletados em Tutuapa, Guatemala, em modelos animais utilizados no *screening* de substâncias psicoativas. **Métodos:** Para os experimentos foram utilizados camundongos Swiss fêmeas (25 a 35g), obtidos do Biotério Central da UNIVALI. Os protocolos experimentais foram submetidos e aprovados pelo CEP/ UNIVALI (Parecer 3008-2007). O EH (50, 100 e 150 mg/kg) foi administrado por via oral em todos os experimentos sendo os efeitos avaliados 60 min após os tratamentos. Para avaliar o efeito antidepressivo da planta, foi utilizado o modelo da natação forçada (MNF), onde os animais foram tratados com o EH, veículo (salina 0,10 mLs/10g), e imipramina (IMI/5mg/kg, v.o.), registrando-se o tempo de imobilidade (TI) e agitação (TA) durante 6 minutos. Para investigar o efeito ansiolítico, foi utilizado o teste do Labirinto em Cruz Elevado (LCE). Animais tratados com EH, diazepam (0.75 mg/kg, i.p.) e veículo, tiveram frequência de entradas nos braços abertos (FEA) e fechados (FEF) e o tempo de permanência nos braços abertos (TPA) e fechados (TPF) avaliados durante 5 minutos. O efeito hipnótico do extrato foi avaliado através do modelo do sono induzido por barbitúrico (MSB). Nesse experimento os animais receberam veículo, EH e Lorazepam (LZP/ 0,75mg/kg, v.o.), 60 min após os tratamentos, receberam pentobarbital, (50mg/kg, i.p.) e, imediatamente após a aplicação do PEN foi cronometrado para cada animal a latência para o sono (LPS) e o tempo total de sono (TTS). **Resultados e Discussão:** A análise de variância (ANOVA) seguida pelo teste Dunnet ($p<0,05$) demonstrou que no MNF, o extrato em todas as doses utilizadas e o controle positivo, produziram diminuição do TIM quando comparado com o controle (VEIC/ 99 ± 18; EH 50 64 ± 17; EH 100 35 ± 7; EH 150/ 26 ± 8; IMI / 13 ± 2). No modelo do LCE, houve um aumento na porcentagem do TPA nos animais que receberam o extrato (50 e 150 mg/kg) e o diazepam quando comparado com o controle (VEIC/ 38 ± 20; EH50mg/kg/ 55 ± 11; EH150 55 ± 14; DZP/ 74 ± 10). Também se observou aumento na FEA (VEIC/ 39 ± 8; EH 150 mg/kg/ 54 ± 7; DZP/ 63 ± 15). No MSB o extrato promoveu diminuição da latência para o sono (VEIC/ 726 ± 234; EH 50 206 ± 42; EH100 174 ± 40; EH150 103 ± 36; LZP/ 106 ± 40) e aumentou o tempo total do sono de forma significativa (VEIC/ 2157 ± 410; EH 50 3512 ± 197; EH100 3464 ± 302; EH 150 3387 ± 475; LZP/ 3507 ± 206). Os resultados obtidos, embora sejam preliminares, nos permitem concluir que a planta em estudo exibe efeito antidepressivo, ansiolítico e hipnótico em animais, validando em parte o uso popular no tratamento da depressão, ansiedade e insônia. Outros experimentos serão necessários para determinação dos constituintes químicos responsáveis por tais efeitos farmacológicos bem como seus respectivos mecanismos de ação. Apoio financeiro: PIBIC/CNPq, Consejo Nacional de Ciencia y Tecnología (FODECYT 102-2006), Rede 0286 RIBIOFAR/CYTED/CNPq.

03.034

Prostaglandinas induzem o comportamento doentio provocado por lipopolissacarídeo em camundongos. Paiva VN, Fernandes, MM, Lima, SNP, Giusti-Paiva A UNIFAL - Ciências Biomédicas

A ativação do sistema imune por endotoxinas resulta em várias alterações comportamentais, que são coletivamente chamadas de comportamento doentio, e o objetivo deste trabalho foi avaliar a participação das prostaglandinas neste modelo experimental. Foram utilizados camundongos machos pesando entre 25 a 35g. Os animais (n = 8-10 por grupo) foram pré-tratados com Veículo (Tris 0,1M pH 8), Indometacina (INDO; 5 mg/kg, inibidor não-seletivo das COX), Nimesulide (NIME; 5 mg/kg, inibidor preferencial da COX 2) e Dexametasona (DEXA; 1 mg/kg, glicocorticóide). Trinta minutos após, os animais foram tratados com salina ou LPS (100 µg/kg, ip). Duas horas após a administração de veículo ou LPS os animais foram submetidos aos testes nado forçado, campo aberto e claro-escuro. No teste do campo aberto, camundongos foram colocados no centro da arena, e foi avaliado o número de linhas dos quadrantes atravessados pelos camundongos durante 5 minutos. Neste teste, foi observada uma redução do número total de linhas cruzadas após a administração de veículo + LPS (48,8 ± 9,6; $p<0,001$) quando comparado com o grupo controle (107 ± 9,3). Os pré-tratamentos com INDO, NIME ou DEXA revertem este efeito do LPS (87,0 ± 8,7; 87,3 ± 10 e 83,0 ± 5,4 respectivamente; $p<0,05$), porém não provocam alteração nos animais tratados com salina (87,0 ± 8,7; 87,3 ± 10 e 83,0 ± 5,4 respectivamente; $p<0,05$). No teste do claro-escuro, os camundongos foram colocados no lado claro e o número de transições entre os dois compartimentos foi avaliado por um tempo de 5 minutos. Neste teste, o LPS provocou uma redução do número de transições (de 12,1±1,3 para 2,8±0,8; $p<0,05$). Os pré-tratamentos com INDO, NIME ou DEXA revertem este efeito do LPS (7,1±0,7; 7,6±1,2 e 9,5±1,8 transições respectivamente; $p<0,05$), sem provocar alterações nos animais tratados com salina. No nado forçado, os camundongos foram colocados em um recipiente com água (25ºC) por um tempo de 6 minutos. Neste teste o LPS provocou um aumento no tempo de imobilidade (de 87±7 para 162±10 s; $p<0,001$). Os pré-tratamentos com INDO, NIME ou DEXA revertem este efeito do LPS (104±12; 106±15 e 114±6 s respectivamente; $p<0,01$), sem provocar alterações nos animais tratados com salina. A reversão do estado doentio pela INDO, NIME e DEXA sugere que as prostaglandinas estão envolvidas nas alterações comportamentais observadas em camundongos sépticos. Apoio Financeiro: FAPEMIG, CNPq

03.035

Different forced swimming protocols induce distinct responses to imipramine in mice.

Centurião FB, Stein AC, Betti AH, Rates SMK FF-UFRGS - Psicofarmacologia

Introduction: The forced swimming test (FST) was introduced by Porsolt *et al.,* (*Eur J Pharmacol* 47: 379, 1978) as an animal model sensible to the treatment with antidepressant drugs and, lately, considered as a depression experimental model. The basic paradigm consists that rats and mice forced to swim in an inescapable form in a restricted space become immobile after vigorous activity. This immobility behavior was interpreted by Porsolt as a motivation loss (behavioral despair). The aim of this study was to compare different FST protocols. **Methods:** Adult male CF1 mice (FEPPS-RS) were treated with vehicle (1mL/100g, p.o.) or imipramine (20-30 mg/kg, p.o.). Immobility time (second) was registered during six minutes. Four protocols were used: P1 – single swimming session with acute treatment one hour before testing; P2 - pretest and test with acute treatment (one hour before second swimming session); P3 - pretest and test with three administrations (5 min, 19 and 23h after first swimming session), all of them using a square pool (20x35cm, 19cm deep, 22 ± 1 ^{o}C); P4 - single swimming session with acute treatment one hour before testing using a cylinder pool (10cm diameter, 13cm deep, 22 ± 1 ^{o}C). All protocols used were approved by UFRGS Research Ethical Committee (project number 01-588). **Results and Discussion:** In P1, there was not a significant difference between vehicle and imipramine (vehicle: test: 90s±19,17; imipramine: test: 78,6s±21,33). The same was observed in P2 (vehicle: pretest 137s±24,9; test: 189,8s±21,2; imipramine: pretest 141,8±19,7; test: 161,4±12,8), as well as in P3 (vehicle: pretest: 173,1s±17,7; test: 235,7s±24,3; imipramine: pretest: 193,2s±11,2; test: 229s±19). Otherwise, it was observed a significant difference between vehicle and imipramine in P4 (vehicle: test: 177,1s±12; imipramine: test: 114,3s±20,8). These values represent the mean immobility time + S.E.M. Statistical analyses were performed by t-test or two-way RM ANOVA, followed by a Dunnett's test. These results suggest that animals learn to become immobile after a pretest session. It can be discussed the different apparatus used: the square pool has a bigger water volume, and it can be interpreted as an environment more aversive to the animal, so it will give up swimming sooner. It was also observed a different behavior: they quit swimming in a rotational manner - witch is the normal behavior - once they hit the pool walls and corners. With these results, we suggest that the square pool is not appropriate for a depression test. **Financial support:** CNPq, CAPES.

03.036

Reversible inactivation of the medial prefrontal cortex impairs aversive memory acquisition in rats. Stern CAJ, Santos CJPA, Bertoglio LJ UFSC - Farmacologia

Introduction: The medial prefrontal cortex (mPFC) is a structure considered to do an interface between emotional and cognitive aspects. Studies using rats with mPFC permanent lesion have reported attenuated defensive responses in fear conditioning model and reduced passive avoidance in step-down task. In order to substantiate these findings, here we sought to investigate whether a reversible mPFC inactivation would impair the acquisition, consolidation and/or retrieval of an aversive memory displayed on trial 2 of rats already experienced in the elevated plus-maze apparatus. It is worth mentioning that the trial 1/trial 2 protocol has proven to be suitable to evaluate either anxiety or memory processes in the same animal. **Methods:** Male Wistar rats (Animal Ethics Committee: 04521/2008 – 7 UFSC) were bilaterally-implanted with guide cannulas aimed at the mPFC. One-week later, they were allocated to six groups (n = 6-10/group) based on the drug treatment [phosphate buffered saline (vehicle) or 1.0 mM of cobalt chloride in 0.2 µl/side] and the moment of these infusions (pre-trial 1, post trial 1 or pre-trial 2) into the mPFC. Behavioral measures scored during 5 min in both trial 1 and trial 2 were the percentage of open-arms time (%OAT), the percentage of open-arms entries (%OAE), stretched-attend postures (SAPs) and enclosed-arms entries (EAE). **Results:** Repeated-measures analysis of variance followed by Newman-Keuls test ($p<0.05$) showed an increase in %OAE [$F(1,18) = 5,78$; $p<0.05$] on trial 2 of elevated plus-maze experience rats infused with 1.0 mM of cobalt chloride pre-trial 1 (35 ± 8) when compared to controls (5 ± 3). When this synaptic blocker was infused into the mPFC post-trial 1 [$F(1,12) = 0,14$; $p=0.72$] or pre-trial 2 [$F(1,13) = 0,01$; $p=0.99$], however, no significant changes in open-arm exploration were observed on trial 2 [%OAE = 15 ± 8 (vehicle), 15 ± 5 (cobalt chloride) and 15 ± 7 (vehicle), 15 ± 8 (cobalt chloride), respectively]. In all cases, no statistically significant differences were observed for %OAT, SAPs and EAE. **Discussion:** The reversible inactivation of the mPFC impaired the acquisition, but not the consolidation or the retrieval of an aversive memory observed on trial 2 of elevated plus-maze-experienced rats. The present results reinforce a role for the mPFC in aversive memory processing. **Financial support**: CNPq, CAPES, FAPESC and FAPESP.

03.037

Social isolation stress in adolescent rats induces behavioral sensitization to amphetamine. Assembleia TLS, Marin MT, Leão RM, Cruz FC, Planeta CS FCF-UNESP-Araraquara - Princípios Ativos Naturais e Toxicologia

Introduction: It is widely accepted that early environmental events may affect the response to psychotropic drugs. The first contact with drugs of abuse usually occurs during adolescence. Repeated exposure to psychostimulant drugs may engender an progressive increase in its locomotor effect. This phenomenon is called behavioral sensitization and is related to the sensitization of dopamine mesolimbic system and has been implicated in the development of drug addiction and drug-induced psychosis. Chronic exposure to stress has been shown to induce behavioral sensitization to psychostimulant drugs. In this context social isolation of rats during the adolescence is a relevant paradigm for studying the effects of early life stress on behavioral sensitization. **Objective:** The present study examined whether adolescent rats exposed to social isolation may show behavioral sensitization to amphetamine. **Methods:** Male Wistar rats were raised from postnatal day (P) 26 to 41 either alone (isolated) or in groups of four per cage (grouped). The expression of sensitization was assessed by a challenge injection of saline or amphetamine (1 mg/kg; i.p.) one day after the last isolation session on P42. The results are expressed as mean ± SEM (n=7-9) and analyzed by ANOVA followed by Newman-Keuls post hoc test. The experimental protocol was approved by the Ethical Committee for use of Human or Animal Subjects of the School of Pharmaceutical Science - UNESP (CEP-13/2004). **Results:** ANOVA showed significant effect of isolation stress [$F(1,27)=4.97$; $p<0.05$)], drug challenge [$F(1,27)=15.06$; $p<0.001$)] and interaction between factors [$F(1,27)=8.21$; $p<0.01$)]. Post hoc analysis showed that adolescent rats exposed to isolation stress displayed higher locomotor response to amphetamine (1755±179) when compared to grouped rats (890±227), $p<0.01$. Locomotor response to saline was not changed in isolated (609±140) compared to grouped (717±137) rats. Moreover, in grouped rats amphetamine injection did not enhance the locomotor activity (890±227) when compared to saline administration (717±137). **Conclusion**: Our results indicated that exposure to social isolation caused the expression of behavioral sensitization to amphetamine. Thus stress can increase de risk of development of addiction in adolescents.

03.038

LASSBio-1412 and LASSBio-1413: N-phenylpiperazine derivatives with potential antipsychotic activity. Betti AH[1], Stolz, ED[2], Neves G[3], Stein AC[3], Martins TS[4], Vieira RO[5], Barreiro EJ[4], Fraga CAM[4], Noel F[6], Rates SMK[1] - [1]UFRGS - Ciências Farmacêuticas, [2]UFRGS - Psicofarmacologia, [3]UFRGS - Farmácia, [4]LASSBio-UFRJ - Farmácia, [5]UFRJ - Farmacologia Celular e Molecular , [6]UFRJ - Farmacologia Básica e Clínica

Introduction: Considering the necessity of an antipsychotic more effective and safer to treat schizophrenia, a series of N-phenylpiperazine derivatives was planned through molecular hybridization between clozapine and L-741 prototypes (Menegatti *et al., Bioorg Med Chem.* 11(22): 4807, 2003) by the *Avaliação e Síntese de Substâncias Bioativas* Group from UFRJ (LASSBio-1412, LASSBio-1413, LASSBio-1414, LASSBio-1415 and LASSBio-1422). The aim of this study was to select the derivatives with potential antipsychotic activity through apomorphine-induced climbing. Also evaluate their potential extrapyramidal side-effects and neurotoxicity by catatonia and rota-rod tests. And finally verify their receptor affinity profile through binding assays. **Methods:** Adult male Wistar rats were used for *in vitro* assays. Binding assays for D2-*like,* 5-HT1A and 5-HT2A receptors were performed using [^{3}H]-YM-09151-2 0,1nM, [^{3}H]-8-OH-DPAT 1nM and [^{3}H]-ketanserin 1nM, respectively. Adult male CF1 mice (FEPPS-RS) were used for *in vivo* assays. All the compounds (15 mg/kg, p.o.) were initially selected by apomorphine-induced climbing and only the active compounds that were able to inhibit climbing were submitted to catatonia and rota-rod tests. All protocols used were approved by UFRGS Research Ethical Committee (project number 2007975). **Results and Discussion:** All tested compounds showed a moderate affinity for D2-*like*, 5-HT1A and 5HT2A receptors, excluding LASSBio-1415 and LASSBio-1422. LASSBio-1413 presented the highest affinity for all receptors. LASSBio-1412, LASSBio-1413 and LASSBio-1414 have a multireceptor profile similar to those of modern atypical antipsychotics. The IC50 for D2-*like,* 5-HT1A and 5-HT2A receptors were: LASSBio-1412: 22.7 μM; 13.3 μM; 27 μM. LASSBio-1413: 2.33 μM; 0.95 μM; 25.7 μM. LASSBio-1414: 10.4 μM; 17.1 μM; 30 μM. LASSBio-1415 and LASSBio-1422: > 30 μM; >30 μM; >30 μM, respectively. LASSBio-1412, LASSBio-1413 and LASSBio-1422 inhibited climbing (vehicle: 10.8±0.5; apomorphine: 17.5±0.3; LASSBio-1412: 10±1.8; LASSBio-1413: 13.6±1.3; LASSBio-1422: 13.9±1.6). They did not induced any catatonic sign at 30, 60 and 90 minutes after treatment, respectively (vehicle: 0.9±0.1; 1.1±0.1; 2.2±0.6; haloperidol: 14.9±5.7; 35±11.5; 58.8±1.2; LASSBio-1412: 1±0.2; 0.7±0.1; 1±0.2; LASSBio-1413: 1.3±0.5; 1.6±0.5; 0.9±0.1; LASSBio-1422: 1.6±0.5; 4.1±1.3; 4.1±1.2). Neither impaired rota-rod performance (time permanence and number of falls, respectively: vehicle: 230.6±21; 1.1±0.5; haloperidol: 79.2±23.9; 15.2±3.8; LASSBio-1412: 227.9±24.4; 4.9±3.6; LASSBio-1413: 240.2±24.1; 1±0.4; LASSBio-1422: 274±15.1; 0.7±0.4). In conclusion, these results demonstrated that the derivatives LASSBio-1412 and LASSBio-1413 are promising molecules to antipsychotics development, once they were active in an animal model predictive to schizophrenia positive symptoms and did not affect the motor coordination. Also, they presented a multireceptor profile characteristic of modern atypical antipsychotics. **Financial support:** CAPES, INCT-INOFARMED/CNPq.

03.039

Antidepressant-like effect of hyperoside, a flavonoid isolated from south Brazilian native *Hypericum* species in rats: involvement of the dopaminergic system. Haas JS[1], Stolz, ED[2], Stein AC[1], Braga A[1], von Poser GL[1], Rates SMK[1] [1]UFRGS - Ciências Farmacêuticas, [2]UFRGS - Neurociências

Introduction: It has been shown that a flavonoid enriched fraction from *Hypericum perforatum* was active in the Forced Swimming Test (FST) (BUTTERWECK *et al*., *Planta Med*., 66:3, 2000). The main compounds isolated from this fraction, including hyperoside, demonstrated anti-immobility effect in the FST. This compound was found in all the South Brazilian *Hypericum* species analysed and could contribute for the antidepressant activity detected in the crude methanolic extract from *H. caprifoliatum* (DAUDT *et al*., *Phytoter Res*., 14, 344, 2000). Previous experiments carried out in our laboratory demonstrated that some phenolic compounds isolated from *Hypericum* native species exert their pharmacological action *via* dopaminergic system (VIANA *et al*., *Neuropharmacol.,* 49, 1042, 2005). Thus, the present study aimed to investigate the possible involvement of D2-like (sulpiride) dopamine receptors of hyperoside in the antidepressant-like activity using the forced swimming test in rats. **Methods:** The aerial parts from *H. caprifoliatum* were submitted to maceration with solvents in increasing polarity. The flavonoid hyperoside (HYP) was isolated from the methanolic extract by silica gel column chromatography and identified by ^{1}H RMN and ^{13}C RMN. For the preclinical study, adult male rats from FEEPS breeding colony were used. The antidepressant-like effect of hyperoside (1.8 mg/kg/day p.o.) was evaluated by the Porsolt's procedure with minor modifications. The animals were forced to swimm for 15 minutes in water with temperature of 22 ± 1 °C and height of 30 cm. The treatments were administered 5 min, 19h and 23h after the first swimming exposition. The animals were submitted to a second swimming session 1 hour after the last administration, and the immobility time was measured for 5 min (results expressed in seconds). To asses the possible involvement of the dopaminergic system, animals were pretreated with sulpiride (50 mg/kg i.p.) 30 min previous to the test session. All data were expressed by mean ± standard deviation and analyzed by ONEWAY ANOVA ($P < 0.05$). All experimental protocols were approved by UFRGS Ethical Committee (Nº2008008). **Results and Discussion:** The flavonoid HYP proved to be effective when compared to vehicle (saline + 1% polysorbate 80) (HYP: 63.62 ± 12.64 s; VEH: 134.06 ± 14.6 s) on the FST. Sulpiride did not affect the immobility time (VEH+SULP: 154 ± 29.47 s). The anti-immobility effect of HYP was reversed by sulpiride (50 mg/kg) (HYP+SULP: 261.5 ± 20.32 s). In conclusion, the results obtained in our work strengthen that hyperoside is, at least in part, responsible for the previously reported antidepressant activity of the crude methanolic extract of *H. caprifoliatum*. The flavonoid effect is mediated by the dopaminergic neurotransmition involving D2-like dopamine receptors. ACKNOWLEDGMENTS: CNPq for the financial support

03.040

FPT-2, FPT-4, FPY-3: triazol and pyrazol N-benzyltiazolidine derivatives with potential antipsychotic activity. Betti AH[1], Stolz, ED[2], Vieira RO[3], Fraga CAM[4], Noel F[5], Lima MCA[6], Galdino SL[6], Pitta IR[6], Rates SMK[7] [1]UFRGS - Ciências Farmacêuticas, [2]UFRGS - Psicofarmacologia, [3]UFRJ - Farmacologia Celular e Molecular, [4]UFRJ - Farmácia - LASSBio, [5]UFRJ - Farmacologia Básica e Clínica, [6]UFPE - Antibióticos, [7]UFRGS -

Introduction: More than 20 antipsychotic drugs are available for clinical use but they cause serious adverse effects and at least one third of the patients are refractory to treatment (Ascher-Svanum *et al.* **Schizophr Bull.** 21:1, 2007). Considering the necessity of more effective and safer antipsychotics, a series of triazol and pyrazol N-benzyltiazolidine derivatives were planned by the Therapeutic Innovation Group from UFPe (FPY-1, FPY-2, FPY-3, FPY-5, FPY-6, FPT-1, FPT-2, FPT-4, FPW-1). The aim of this study was to select the derivatives with potential antipsychotic activity through apomorphine-induced climbing and to evaluate their potential extrapyramidal side-effects and neurotoxicity by catatonia and rota-rod tests as well as verify their receptor affinity profile through binding assays. **Methods:** Adult male Wistar rats were used for *in vitro* assays. Binding assays for D2-*like,* 5-HT1A and 5-HT2A receptors were performed using [^{3}H]-YM-09151-2, [^{3}H]-8-OH-DPAT and [^{3}H]-ketanserin, respectively. Adult male CF1 mice were used for *in vivo* assays. All compounds (30 mg/kg, p.o.) were tested in apomorphine-induced climbing, and only the active compounds were submitted to catatonia and rota-rod tests. The doses were chosen based on results from N-phenylpiperazine isosters (Neves *et al*. *Pharmacol Biochem Behav*.89:23, 2008). All protocols used were approved by UFRGS Research Ethical Committee (project number 2007975). **Results and Discussion:** All derivatives have very low affinities for D2-*like,* 5-HT1A and 5-HT2A receptors since at 10μM they did not cause any significant binding inhibition to these sites. The exception is FPY-3 at 5-HT2A receptor (IC50=11.4μM). Results from *in vivo* tests showed that FPT-2, FPT-4 and FPY-3 inhibited climbing (vehicle: 8.5±0.6; apomorphine: 17.7±0.2; FPT-2: 9.1±0.8; FPT-4: 12.2±2.0; FPY-3: 13.8±1.4). They did not induce any catatonic sign at 30, 60 and 90 minutes after treating, respectively (vehicle: 1.2±0.2; 1.4±0.3; 1.7±0.3; haloperidol: 14.9±5.7; 35±11.5; 58.8±14.5; FPT-2: 2.3±0.7; 7.5±3.6; 7.5±2; FPT-4: 2.5±0.7; 3.7±1.6; 6±2.6; FPY-3: 1.6±0.4; 1.5±0.3; 4.5±1.5). Neither impaired rota-rod performance (time permanence and number of falls, respectively: vehicle: 233±21.7; 1.0±0.5; haloperidol: 79.2±24; 15.2±4; FPT-2: 250±24.4; 4.5±4; FPT-4: 199±26.1; 3.5±1.5; FPY-3: 213±31.5; 1.7±0.8). Among them, FPY-3 was chosen to continue the study. A climbing dose-response curve (5, 15 and 30 mg/kg, p.o.) indicated that 15 mg\kg was the minimal effective dose. FPY-3 did not affect any parameter observed in the open field (crossings, rearings and groomings) at the highest dose demonstrating that it does not present sedative effect at this dose. In conclusion, these results demonstrated that FPT-2, FPT-4 and FPY-3 are active on climbing behavior induced by apomorphine, a model of schizophrenia positive symptoms, without affecting motor coordination, making them promising molecules for antipsychotic development. Furthermore as they did not present high affinities for D2-*like,* 5-HT1A and 5-HT2A receptors they could act by other mechanism than usual atypical antipsychotics. **Financial support:** PROCAD-CAPES, INCT-INOFARMED/CNPq.

03.041

Clozapine reverses the immobility time increase induced by repeated forced swimming.

Neves G[1], Antonio CB[1], Pranke M[2], Grazziotin LR[2], Betti AH[1], Rates SMK[1] [1]UFRGS - Ciências Farmacêuticas, [2]UFRGS - Farmácia

Introduction: The immobility behavior induced by a single exposition to forced swimming has been considered as a measure of depression in rodents and used for screening antidepressant molecules. Acute administration of NMDA receptor antagonists (such as ketamine) is able to reduce this immobility pointing to an antidepressant-like effect. On the other hand, some studies showed that repeated treatment with phencyclidine increases the immobility time of mice exposed repeatedly to forced swimming. This effect has been considered similar to negative symptoms of schizophrenia since it was selectively prevented by atypical (Noda *et al. Br J Pharmacol* 116 (5): 2531, 1995). Based on results from phencyclidine we decided to evaluate the effect of repeated treatment with ketamine on mice immobility time submitted to chronic forced swimming aiming to develop an animal model of symptoms of schizophrenia. **Methods:** Male CF1 mice from FEPPS-RS breeding colony were used (Etical approval – Comitê de Ética em Pesquisa UFRGS protocol 2006541). Animals were forced to swim for three minutes (15 cm dept, 21 ± 1°C). The immobility time was measured one day before any treatment (D0), and 1 (D1), 3 (D3), 7 (D7), 14 (D14) and 21 (D21) days after different treatment schedules. Saline 1mL/kg i.p. (SAL) and ketamine 30 mg/kg i.p. (KET) during 14 days were selected for further evaluation. The effect of clozapine (CLO 10 mg/kg p.o.) and imipramine (IMI 20 mg/kg p.o.) on the immobility behavior was investigated. These same drugs and ketamine (30 mg/kg p.o.) were also evaluated in the classical Porsolt forced swimming test. **Results and Discussion:** According to literature data, ketamine, imipramine and clozapine reduced the immobility in the Porsolt test (SAL = 134 ± 15 s; KET = 52 ± 5 s; CLO = 60 ± 10 s; IMI = 39 ± 9 s) demonstrating that our laboratory conditions are adequate to detect anti-immobility effects. In the repeated forced swimming protocol, animals' immobility increased across the days, reaching at maximum 7 days after the treatment interruption both in ketamine and saline groups (SAL – D0 = 25 ± 6 s; D1 = 68 ± 7 s; D3 = 87 ± 12 s; D7 = 92 ± 13 s; D14 = 85 ± 9 s; D21 = 85 ± 13 s; KET one day of treatment - D0 = 34 ± 10 s; D1 = 61 ± 11 s; D3 = 79 ± 9 s; D7 = 91 ± 12 s; D14 = 89 ± 10 s; D21 = 70 ± 9 s; KET for five days - D0 = 31 ± 7 s; D1 = 49 ± 9 s; D3 = 67 ± 11 s; D7 = 89 ± 12 s; D14 = 67 ± 11 s; D21 = 66 ± 10 s; KET for fourteen days - D0 = 35 ± 7 s; D1 = 40 ± 7 s; D3 = 82 ± 12 s; D7 = 90 ± 12 s; D14 = 87 ± 14 s; D21 = 74 ± 13 s). Ketamine administration did not influence immobility acquisition profile. Clozapine but not imipramine presented an anti-immobility effect in animals treated with ketamine as well as saline (SAL+SAL = 50 ± 14 s; SAL+IMI = 48 ± 8 s; SAL+CLO = 19 ± 6 s; KET+SAL = 65 ± 36; KET+IMI = 66 ± 10 s; KET+CLO = 7 ± 2 s) suggesting that the immobility behavior developed after repeated swimming is sensible to antipsychotics preferentially. These results point to the usefulness of repeated forced swimming protocol for developing new animal models predictive of antipsychotic action. **Financial support:** FAPERGS; INCT de Fármacos e Medicamentos, INOFARMED, CNPq.

03.042

Modafinil induces conditioned place preference in mice. Borçoi A.R[1], Wuo-Silva R[1], Sanday L[1], Fernandes HA[1], Leite JMC[1], Lasagno CMR[1], Bittencourt LRA.[2], Frussa-Filho R[1] [1]UNIFESP - Pharmacology, [2]UNIFESP - Psychobiology

Introduction: Modafinil is a wake-promoting agent used in the treatment of excessive daytime sleepiness in narcolepsy. Despite the controversial literature, it has been reported that modafinil possesses a reduced abuse potential. The purpose of the present work was to investigate a potential addictive effect of modafinil on the conditioned place preference paradigm. **Methods:** Thirty-six female Swiss mice were allocated in three groups (n=12): Saline (Sal), Modafinil 64 mg/kg (Mod64) and Modafinil 128 mg/kg (Mod128) and submitted to an unbiased place preference conditioning session. Conditioning sessions were conducted twice daily with a minimum interval of 6 hours from one another. All the animals were injected with saline or modafinil (i.p.) and 30 min later confined to one of the compartments of the place preference apparatus for 10 minutes. Treatment compartment was counterbalanced for saline and modafinil, as well as the presentation order of saline and modafinil. Test sessions for the evaluation of conditioned behavior were conducted 24 hours after the last conditioning session and each animal was tested only once. During test sessions, uninjected mice were allowed free access to both compartments of the place preference apparatus for 15 minutes. The experiment was approved by the Research Ethics Committee of the Federal University of São Paulo (UNIFESP), number: 1724/08. **Results:** The paired T-test showed that mice of the groups Mod64 and Mod128 groups presented increased in the time spent in the drug-paired compartment (607±41 and 421±47, respectively) when compared to the saline-paired compartment (176±29 and 249±34, respectively). Similar results were observed in the other parameters, locomotor activity in the drug-paired compartment (70±6 and 73±8, respectively) in comparation with saline-paired compartment (40±6 and 49±8) and number of entries in the drug-paired compartment (20±3 and 23±2 respectively) in comparison with saline-paired compartment (15±2 and 16±1, respectively). **Discussion:** Our results showed that modafinil-treated animals presented a conditioned place preference, indicating the potential addictive effect of this drug. **Financial Support:** CAPES and CNPq

03.043

The role of EAG-1 potassium channels in the *startle* response and prepulse inhibition.

Fonseca JR[1], Issy Pereira AC[2], Del Bel EA[1] [1]FORP-USP - Morfologia, Estomatologia e Fisiologia, [2]FMRP-USP - Farmacologia

Introduction: Prepulse inhibition (PPI) refers to a decrease in the magnitude of startle response that is observed when the loud noise is preceded by a weak acoustic stimulus (a "prepulse"). PPI disruption is seen in schizophrenia and can be induced in rodents by dopamine releasers and agonists. This effect is reversed by antipsychotics. Recently, studies had demonstrated that some antipsychotic drugs (dopaminergic antagonists) present the ability to block genes of the potassium channel of ether-a-go-go family, including the EAG-1. Previous results from our group demonstrated the expression of EAG-1 potassium channel in the dentate gyrus of hippocampus. The role of EAG-1 potassium channel on PPI is unknown. According to the described, the objective of this work is to analyze the role of EAG-1 potassium channel in dentate gyrus of hippocampus of *Wistar* rats in the startle response and prepulse inhibition. In order to do that we used the EAG-1 monoclonal *single-chain* antibody. **Methods**: Male *Wistar* rats were submitted to stereotaxic surgery to bilateral hippocampus cannulae (9mm) implantation. After surgery the most of animals showed PPI disruption. For this reason the animals were divided in two groups. The first one that showed PPI disruption was treated with intracerebral EAG-1 antibody (0.5 or 1µg/µl; 0,2µl; 5 minutes before the PPI test) or with systemic injection of haloperidol (1 or 2 mg/kg; one hour before test). The second group that showed positive PPI response was treated with apomorphine (0.5mg/kg; subcutaneous) preceded or not by EAG-1 antibody. The PPI test consist of 64 trials irregularly divided into pulse (P, white noise, 100 dB), prepulse (pure tone; 3kHz; 69, 73 or 81 dB), prepulse+pulse (PP) and no-stimuli– %PPI=[100-(PP/P)*100]. The percentage of PPI was analyzed with repeated measures (MANOVA) with the treatment as the independent factor and the prepulse intensity as repeated measure. Duncan´s post hoc test ($p<0.05$) was used to specify differences revealed by significant MANOVAS. **Results:** Either EAG-1 antibody and the antipsychotic haloperidol reversed the PPI disruption in a dose dependent manner (Duncan, $p<0.05$). The disruption of PPI induced by apomorphine was not modified by the EAG-1 channel block. The startle response amplitude was not modified by any of treatments. **Discussion:** The ability of EAG-1 antibody to modify the PPI response suggests that the EAG-1 potassium channel may have a role on PPI control. This effect was similar to that of the antipsychotic haloperidol. The EAG-1 antibody did not affect the motor system given that the startle response was not influenced. Additional studies are necessary to clarify the role of EAG-1 potassium channel on PPI control. **Supported by**: FAPESP and CNPq. **Ethical Committee number:** 057/2008

03.044

Interações agudas entre a associação chá de ayahuasca com propofol observadas em modelos animais. Pires JM[1], Mendes FR[2], Amaral JL G do[1], Carlini ELA[2] [1]UNIFESP - Anestesiologia, Dor e Medicina Intensiva, [2]CEBRID-UNIFESP - Psicobiologia

Introdução: O chá de ayahuasca (AYA) é utilizado em práticas ritualísticas por nativos da Amazônia e possui propriedades psicoativas. É composto por duas plantas: o cipó *Banisteriopsis caapi* (Spruce ex Griseb.) C.V. Morton (Malpighiaceae) e as folhas de *Psychotria viridis* (Ruiz & Pav.) (Rubiaceae). Diante da crescente popularidade da AYA, existe a necessidade de serem estabelecidos os parâmetros de segurança de uso deste chá com outras drogas, como já foi descrito para alguns fitoterápicos e sucos de frutas. Neste trabalho foi mostrado através de experimentos com animais de laboratório as respostas comportamentais da possível interação do AYA com o propofol. **Objetivos:** Investigar se ocorre interação do chá de AYA com o propofol, um agente muito usado em anestesia geral. Segundo informação de um usuário do chá, é procedimento comum que seja ingerido um copo de chá antes do indivíduo se submeter a uma cirurgia, com a finalidade de diminuir a ansiedade e manter a calma (comunicação pessoal). Até o momento não existem na literatura médica dados que permitam avaliar a segurança do procedimento anestésico em pacientes que façam uso da bebida ayahuasca. **Métodos:** O AYA foi liofilizado e seus efeitos foram avaliados através dos testes do rota-rod (coordenação motora), pelo teste de indução de sono com propofol (ISP) (estimulante/sedativo) e teste de quantificação de *grooming* (QG). Grupos de 5-10 animais cada foram tratados (via oral) com AYA isoladamente (120 mg/kg ou 1X - dose aproximada usada por humanos em ritual e 1200 mg/kg ou 10X), ou combinado com propofol (50, 100, 140 e 175 mg/kg, ip) que também foi administrado isoladamente. Nestes testes camundongos Suíços, machos (3-4 meses, 35-50 g) receberam o liofilizado do AYA 30 min antes do teste, com exceção do teste de quantificação de *grooming*, no qual os animais receberam a 2ª droga aos 60 min. **Comitê de ética:** UNIFESP/nº 1494/06. **Resultados e discussão:** AYA 10X apresentou uma tendência em potencializar a incoordenação motora induzida pelo propofol 100 mg/kg aos 30 min de avaliação no rota-rod. No teste ISP, os animais pré-tratados com AYA 10X e em seguida propofol 175 mg/kg apresentaram aumento do tempo de sono (TS) ($p \leq 0,05$ – ANOVA/DUNCAN). No teste de QG, AYA 10X praticamente inibiu a resposta de *grooming* ($p \leq 0,05$ – ANOVA/DUNCAN). Em contrapartida, propofol 50 mg/kg provocou um aumento do *grooming* ($p \leq 0,05$ – ANOVA/DUNCAN). Já no grupo da associação chá + propofol, observa-se que prevaleceu o efeito do chá, bloqueando o "grooming" produzido pelo propofol ($p \leq 0,05$ – ANOVA/DUNCAN). Em suma, a associação de AYA com propofol apresentou indícios de potencialização do efeito depressor do anestésico, embora de baixa intensidade. O conjunto de resultados indica alguma interação no que se refere à associação do AYA com o propofol. Essas interações foram discretas e necessitariam de experimentação clínica apropriada para verificar sua ocorrência no ser humano. **Apoio Financeiro:** AFIP, FAPESP e Laboratório Cristália.

03.045

Transposition methods of doses obtained from pharmacology pre-clinical to phase 1 clinical trials: antipsychotics as study of case. Antonio CB[1], Dalla Costa T[2], Neves G[1], Centurião FB[1], Rates SMK[1] [1]FF-UFRGS - Psicofarmacologia, [2]FF-UFRGS - Farmacocinética

Introduction: Developing new drugs requires pharmacological studies in animals (pre-clinical) prior studies in humans (clinical). It is an intense study, in which one of the key steps is the decision of what dose is appropriate for first testing in humans according the preclinical studies. **Methods:** Through a search of scientific databases, the methods used to calculate the initial dose for phase 1 clinical trials were reviewed and applied to *N*- fenilpiperazines derivatives LASSBio579 and LASSBio581, antipsychotic candidates, as well as to market antipsychotic drugs: chlorpromazine, clozapine, haloperidol and aripiprazole. The data utilized for predicting calcules were obtained from previous experiments (Etical approval – Comitê de Ética em Pesquisa UFRGS protocol 2006541). For the calculations, were used maximum non toxic doses (induction of extrapyramidal effects and blood discrasia) and effective doses in animal predictive model of antipsychotic effect: apomorphine-induced climbing. **Results and Discussion:** The methods fall into two groups: the group that use toxicology parameters and the group that use pharmacologic parameters. The first group uses the highest non toxic dose in animals (NOAEL) to realize the estimate. The second group utilizes the animal active doses. Based on NOAEL, the first dose for humans of LASSBio579 would be 3 mg and the maximum 37,5 mg; to LASSBio581 the first dose would be in the range 1,5 - 3,0 mg and the maximum between 18,8 – 37,5 mg. Based on active doses, the first dose of LASSBio579 would be in the range 7 – 70 mg. It was not possible to calculate the LASSBio581 first dose based on these methods because LASSBio581 doesn't showed an active dose in the model chosen. This large variation of doses was also observed for the antipsychotic drugs on the market, where the method that most closely approximated the doses used in therapy was the Kuhlman method (1997), based on active doses. **Financial support:** FAPERGS; INCT de Fármacos e Medicamentos, INOFARMED, CNPq.

03.046

Effects of capsazepine administered into the dorsal hippocampus on spatial memory in rats. Scoz-Silva R, Aguiar Jr AS, Bertoglio LJ UFSC - Farmacologia

Introduction: The hippocampus modulates anxiety and the learning/memory process. A relative contribution of its dorsal and ventral poles has been demonstrated: whereas the ventral hippocampus has a key role in the former, the dorsal hippocampus is preferentially involved in the latter. The neurochemical mechanism supporting the regional functional dissociation within the hippocampus still remains to be investigated. As a functionally active population of transient receptor potential vanilloid type 1 (TRPV1) channels occurs in the rat dorsal hippocampus, the present study sought to investigate whether the pharmacological blockade of its TRPV1 channels interferes with the acquisition and/or retrieval of the spatial memory of rats exposed to the water-maze task. **Methods:** Male Wistar rats were bilaterally-implanted with guide cannulas aimed at the dorsal hippocampus. One-week after surgery, each animal was infused with vehicle (phosphate buffered saline containing 15 % of dimethyl sulfoxide) or the TRPV1 channel antagonist capsazepine (1.0 or 3.0 nmol in 0.2 uL per side) 10-min before training or testing in the water-maze. The behavioral measure scored during training was the total time spent to find a hidden platform (TFHP) in 5 consecutive trials while in the test session it was the time spent swimming in the target quadrant (TSTQ), i.e. the one where the hidden platform was located during training. The experimental design aforementioned was approved by the local Ethical Committee in Animal Research (068-2008/CEUA/PRPe/UFSC). **Results**: Repeated-measures analysis of variance followed by Newman Keuls test ($p<0.05$) showed that rats infused into the dorsal hippocampus with capsazepine before training performed this session equally to controls [TFHP: vehicle (mean ± S.E.M.) = 215 ± 31 s; capsazepine 1.0 nmol = 231 ± 32 s; capsazepine 3.0 nmol = 263 ± 25 s]. When 1.0 nmol of capsazepine was infused prior to testing, however, the TSTQ was reduced [vehicle (mean ± S.E.M.) = 29.1 ± 2.3 s; capsazepine 1.0 nmol = 24.4 ± 1.3 s; capsazepine 3.0 nmol = 30.5 ± 2.0 s]. **Discussion**: Rats demonstrated poor spatial memory retrieval during the test session in the water-maze after the bilateral infusion of capsazepine (1.0 nmol) when compared to controls. The present results indicate that the dorsal hippocampus modulates the learning/memory process, and suggest that TRPV1 channels are recruited for this action. **Financial support**: CNPq, CAPES, FAPESP and FAPESC (Brazil).

03.047

Effects of capsazepine administered into the dorsal hippocampus on spatial memory in rats. Scoz-Silva R, Aguiar Jr AS, Bertoglio LJ UFSC - Farmacologia

Introduction: Electrical or chemical stimulation of the dorsal periaqueductal gray matter (DPAG) and dorsomedial hypothalamic nucleus (DMH) induces defensive reactions in laboratory animals, such as escape behavior, that have been related to panic attacks in humans. Furthermore, it was demonstrated that these escape responses could be inhibited by treatment with drugs used in panic disorder. These evidences supported the idea that both DPAG and DMH are directly involved in the pathophysiology of panic disorder (1, 2). Since then, electrical or chemical stimulation of these two brain areas have been used as an experimental model of panic. In relation to DPAG, using the model of electrical stimulation, it has been shown that intra-DPAG administration of 5-HT_{1A} and 5-HT_{2A} receptor agonists inhibit the escape response (3, 4). However, the importance of the serotonergic neurotransmission in the mediation of the escape response induced by electrical stimulation of the DMH is unknown. The present study aims to investigate the effect of intra-DMH injection of 5-HT_{1A} and 5-$HT_{2A/2C}$ receptor agonists on escape response of rats submitted to the electrical stimulation of DMH. **Methods**: Male Wistar rats (250-280 g) were intra-DMH injected (0.2 µl) with 5-HT (20 nmoles), 8-OH-DPAT (8 nmoles), DOI (16 nmoles) or saline. The threshold of aversive electrical stimulation that applied to the DMH evokes escape behavior was measured before and after the microinjection of these agonists. Commission ethical protocol nº 077/2008 – CETEA-FMRP/USP. **Results**: Our data showed that intra-DMH administration of serotonergic agonists significantly raised the intensity of electrical current for inducing escape [Δ threshold (mean ± EPM; µA): saline = 7.69 ± 2.33; 5-HT = 37.54 ± 5.19; 8-OH-DPAT = 36.62 ± 3.20; DOI = 40.31 ± 4.70]. **Discussion**: Our results suggest that the injection of serotonergic agonists into the DMH, such as SCPD, causes a panicolytic effect, via activation of 5-HT_{1A} and 5-$HT_{2A/2C}$ receptors. References: 1. Schenberg LC et al. *Neurosci Biobehav Rev*, 25: 647, 2001; 2. Shekhar A. *Biol Psychiatry*, 36(11): 748, 1994; 3. Nogueira RL and Graeff FG. *Behav Pharmacol*, 2: 73, 1991; 4. Schütz MT et al. *Psychopharmacology*, 85(3): 340, 1985. **Support**: Fapesp and CNPq, Brazil.

03.048

Efeito agudo da *Dioclea violacea* M. sobre os movimentos orofaciais e a atividade geral em ratos observados no campo aberto. Gemignani S, Bertassi C, Pedroso-Mariani SR FMJ - Farmacologia

Introdução: A *Dioclea violacea* M. (DVM) também conhecida como coroanha é usada popularmente na forma de infusões preparadas a partir do pó da semente. É indicada como “calmante para prevenir e remover sequelas do derrame, no tratamento da epilepsia e do mal de Parkinson”. O objetivo deste trabalho foi verificar se a administração aguda de DVM modifica a atividade geral de ratos observados no campo aberto e o efeito sobre a manifestação de movimentos orofaciais. **Métodos**: CEEA - FMJ número: 165/09, Ratos Wistar machos, pesando em média 300 g foram divididos em cinco grupos (n = 8). Vinte minutos antes da observação para quantificação de movimentos orofaciais, isoladamente em gaiolas metálicas, os animais dos grupos experimentais (EXP) foram tratados com a suspensão aquosa do resíduo do extrato alcoólico, evaporado, do pó da semente de DVM nas concentrações de (0,75g/ kg, 1,5g/ kg, 3,0g/ kg, 6,0g/ kg, ip.). Os animais do grupo controle (CON) foram injetados com água destilada (1 ml/ kg, ip). Durante dez minutos foram registradas as freqüências de movimentos orofacias (MOF) e protrusão de língua (PL). A atividade geral no campo aberto foi observada em seguida, trinta minutos após a administração da suspensão da DVM nas concentrações referidas. Os animais do grupo experimental (EXP) e controle (CON) foram observados, por cinco minutos e registradas as freqüências de locomoção (LO), levantar (LE) e a duração de imobilidade (DI) em segundos. **Resultados**: Os animais EXP apresentaram aumento significante da duração de imobilidade nas doses de 0,75g/ kg (média ± desvio padrão = 170 ± 61,8), de 3,0g/ kg (162,25 ± 32,51) e de 6,0g/ kg (241,63 ± 31,37) quando comparados com os animais do grupo controle CON (117 ± 30,5) ($p < 0,05$ Análise de Variância, ANOVA). A locomoção foi menor nos animais EXP na dose de 6,0g/ kg (7,75 ± 3,33) comparado com o CON (42,0 ± 16,86). A frequência de LE aumentou no grupo EXP na dose de 0,75g/ kg (11,50 ± 5,10) e diminuiu na dose de 6,0 g/kg (1,25 ± 0,46) quando comparado com o CON (5,50 ± 2,62). Os movimentos mandibulares em animais EXP na dose de 1,5g/ kg (8,63 ± 3,70) apresentaram aumento significante frente ao CON (3,88 ± 2,85). Não houve diferença significante em relação ao parâmetro de protrusão de língua (PL) nas doses empregadas. Discussão: O efeito da DVM aumentou a duração de imobilidade em três das doses estudadas e reduziu a freqüência de locomoção na dose máxima, sugerindo um efeito importante sobre a atividade motora na dose de 6,0 g/kg. O efeito da DVM aumentou a movimentação orofacial sugerindo também um efeito sobre a atividade motora involuntária. Isso faz pressupor novas perspectivas de investigação em modelos de patologias envolvidas.

03.049

Chronic ingestion of ethanol induces a decrease in the expression of glur1 subunit in hippocampus of rats. Ferreira MBB[1], Dos Santos JM[2], Souto TS[1], Prando N[1], Guidotti FC[1], Cêra NA[1], Iyomasa MM[1], Rosa ML[1] [1]FIPA-FAMECA - Bioquímica, [2]FAMECA - Ciências Fisiobiológicas

Introduction: Long-term alcohol abuse produces serious, harmful effects on a variety of the body's organ systems leading to cognitive, behavioral, motor and neural deficits. Glutamate is involved in both physiological functions and pathological processes of the brain through distinct receptors. Evidence show that AMPA GluR1 subunit plays a role in mediation of synaptic plasticity and cognition impairment. The aim of this work was to investigate the changes induced by chronic ingestion of ethanol on the expression of glutamate AMPA receptors in rat hippocampus. **Methods**: Rats (150g, n=8-12) were housed in a temperature-controlled room (23ºC), on a 12:12-h light:dark cycle, with free access to food and water. They were treated with water (control) or 5%-20% of ethanol, increasing 5% per week (habituation), and 20% maintained for 15, 60 or 90 days (chronic ingestion). After each time all animals were deeply anaesthetized, perfused and their brains removed. 40-mm sections were used for immunohistochemistry: anti GluR1 (Chemicon), secondary antibody (Dako), ABC Kit (Vectastain), DAB (Sigma). Using a light microscope Axioskop 40 with AxioCam ICc3 and AxioVision Release 4.6.3 04-2007, Zeiss, the immunopositive cells were counted in hippocampus, 3 sections/rat, bilaterally. Groups were compared by Student "*t*" test or Anova followed by Duncan test and the level of significance was $p<0.05$. **Results:** Chronic ingestion of ethanol for 90 days induced a significant decrease in the expression of GluR1 AMPA receptors in hippocampus compared to 15 days (21%) and 60 days (29%) of ingestion ($p=0.001$, Anova). However, no change was found when the ethanol groups were compared to control groups in each time, individually. **Discussion:** A decrease in the expression of GluR1 AMPA receptors contribute to the imbalance on glutamatergic neurotransmission in hippocampus induced by long-term ethanol ingestion. **Committee on Animal Research and Ethics**: 02/08 **Financial Support**: Fundação Padre Albino.

03.050

Ayahuasca induces memory impairments in mice. Talhati F[1], Ricardo VP[2], Wuo-Silva R[3], Frussa-Filho R[3], Marinho EAV[4] [1]UBC - Ciências da Saúde, [2]UNIFESP/UNIP – Farmacologia/Ciências da Saúde, [3]UNIFESP - Farmacologia, [4]UBC/UNIFESP - Ciências da Saúde/Farmacologia

Introduction: The use of *ayahuasca*, a hallucinogenic beverage obtained from the decoction of *Banisteriopsis caapi* stems with *Psychotria viridis* leaves, is increasing worldwide. Despite *ayahuasca* widespread use and the relative knowledge of its chemical compounds, few studies have systematically addressed the behavioral effects of its oral administration. In this context, the present work aimed at evaluating the effects of the oral administration of an *ayahuasca* lyophilized extract on anxiety, memory and locomotion in mice, using two different memory paradigms, the step-through inhibitory avoidance and the plus-maze discriminative avoidance task. **Methods:** 3-month old Swiss male mice were used (± 40 g). All the animals were maintained under conditions of controlled temperature (21±2°C) and under a 12 h light/dark cycle with lights on at 7:00 am. Food and water were available *ad libitum* throughout the experiments. The *ayahuasca* beverage obtained from *Santo Daime* cult members was submitted to the freeze-drying process of lyophilization, obtaining a brownish powder, which was then diluted in saline prior to both experiments. In the first experiment, 48 animals were equally allocated to four groups and orally treated with *ayahuasca* (10 ml/kg) in the doses of 30 (AH30), 100 (AH100) and 300 (AH300) mg/kg or saline as the control solution (CTRL). One hour following the treatments all the animals were submitted to the training session of the step-through inhibitory avoidance and 24 hours later to the test session using the same apparatus to evaluate possible cognitive impairments. In experiment 2 different animals were submitted to the same experimental protocol, although this time the plus-maze discriminative avoidance task was used. This animal model has the ability to concomitantly detect bidirectional alterations in anxiety-like behavior, locomotor activity and learning/memory. This work was approved by the Research Ethics Committee of Braz Cubas University, number: 176/2008. **Results:** t-test for paired samples revealed that all animals observed in experiment 1 presented a significant increase in the step-through latency time in the test session when compared to the training session. One-way ANOVA did not show any significant differences between groups in both sessions. Nevertheless, in experiment 2, t-test for paired samples revealed that in the test session all groups, but AH300, spent significantly less time in the aversive enclosed arm when compared to the non-aversive enclosed arm. One-way ANOVA also revealed that the same group presented a significant increase in the percent time spent in the aversive enclosed arm (38.62 ± 11.37) when compared to all other groups (8.18 ± 3.63, 13.62 ± 4.14 and 14.98 ± 3.77 for CTRL, AH30 and AH100, respectively), revealing the amnestic effect of the highest dose of *ayahuasca* when the animals were observed in the plus-maze discriminative avoidance task. No differences were observed in anxiety-like behavior and locomotor activity. **Discussion:** Treatment with 300 mg/kg *ayahuasca* did promote amnestic effects in mice. The difference observed between the experiments showed that the plus-maze discriminative avoidance task is a more sensitive paradigm in the detection of mild memory alterations.

03.051

A expressão da sensibilização comportamental à nicotina em ratos adolescentes e adultos. Garves LA, Cruz FC, Planeta CS FCF-UNESP Araraquara - Princípios Ativos Naturais e Toxicologia

Introduçäo: Estudos demonstram que adolescentes apresentam maior suscetibilidade ao tabagismo. Em ratos, a exposição repetida à nicotina promove sensibilização comportamental. Esta reflete neuroadaptações do sistema mesocorticolímbico que estão relacionados ao desenvolvimento do uso compulsivo das substâncias de abuso. O objetivo desse estudo foi investigar a expressão da sensibilização comportamental à nicotina entre ratos adultos e adolescentes. **Materiais e Métodos:** Ratos Wistar machos adolescentes, dia pós-natal (DPN) 28-42, e adultos, DPN 60, receberam uma injeção diária de nicotina (0,4 mg/kg s.c.) ou salina durante 7 dias. Três dias após o término desse tratamento os animais foram transferidos individualmente para caixa de registro da atividade locomotora por 20 minutos para habituação. Imediatamente após esse período os ratos receberam injeção de nicotina (0,2 ou 0,4 mg/kg s.c.) ou salina e a atividade locomotora foi avaliada por 15 min (teste). Assim foram formados os seguintes grupos para animais adultos e adolescentes: SAL-SAL, SAL-NIC 0,2, SAL-NIC 0,4, NIC-SAL, NIC-NIC 0,2 E NIC-NIC 0,4 Os valores representam a média ± EPM de 5-6 ratos por grupo e foram analisados por ANOVA multifatorial considerando os fatores idade e pré-tratamento, seguido pelo teste Newman-Keuls. Os experimentos foram aprovados pelo Comitê de Ética em Pesquisa da Faculdade de Ciências Farmacêuticas – Unesp (CEP19/2004). **Resultados:** Nossos resultados demonstraram que os ratos adultos e adolescentes que foram pré-tratados com nicotina apresentaram maior atividade locomotora em resposta a administração de nicotina 0,2 e 0,4 mg/kg quando comparados ao grupo pré-tratado com salina ($p<0,05$). [adultos: SAL-SAL (631,5±100,7); SAL-NIC 0,2 (736,6±103,8), SAL-NIC 0,4 (961,0±56,1), NIC-SAL (434,5±191,9), NIC-NIC 0,2 (1237,5±65,1) e NIC-NIC 0,4 (1667,5±160,5); adolescentes: SAL-SAL (534,6±138,4), SAL-NIC 0,2 (991,2±141,3), SAL-NIC 0,4 (1259,0±62,7), NIC-SAL (639,2±205,4), NIC-NIC 0,2 (1720,5±285,8) e NIC-NIC 0,4 (1784±76,5)]. **Discussão:** Assim foi observada a expressão da sensibilização comportamental para as duas doses de nicotina testadas em ambas as idades. **Apoio Financeiro:** PIBIC/CNPq

03.052

Neonatal hypoxia produces dopaminergic hyperresponsiveness to cocaine in adult mice. Ricardo VP[1], Kameda SR[2], Almeida E[2], Wuo-Silva R[2], D´Almeida V[3], Tufik S[3], Frussa-Filho R[2] - [1]UNIP - Biomedicina, [2]UNIFESP - Farmacologia, [3]UNIFESP - Psicobiologia

Introduction: Schizophrenic patients present several behavioral alterations, including a greater prevalence of substance use disorders. A large number of epidemiological studies have now confirmed that obstetric complications clearly associated with fetal or neonatal hypoxia confer increased risk for schizophrenia. In this context, the objective of this study is to verify the long-term effects of neonatal hypoxia on cocaine-induced behavior. **Methods:** Reactivity to novelty, cocaine-induced behavioral sensitization and locomotor conditioned response (animal models of drug abuse) were used to evaluate the behavior of fourteen hypoxic and fourteen non-hypoxic female mice. This work was approved by the Research Ethics Committee of São Paulo Federal University, number: 0776/06. **Results:** Neonatal hypoxia produced an increase in the reactivity to a novel environment (4726.14 $\pm$ 202.39 and 4006.62 $\pm$ 239.64 for neonatal hypoxia and control groups, respectively), an enhancement in the cocaine-induced behavioral sensitization (7735.69 $\pm$ 280.22 and 6395.69 $\pm$ 347.78 for neonatal hypoxia and control groups, respectively) and facilitation in the establishment of a conditioned locomotor response (5165.38 $\pm$ 233.22 and 4331.25 $\pm$ 311.95 for neonatal hypoxia and control groups, respectively). **Discussion:** Locomotor activity in rodents has been extensively related to the activity of the mesolimbic dopaminergic system, which plays a critical role in both schizophrenia and drug dependence. Within this context, the present study supports the possibility that schizophrenic patients present an increase in the prevalence of substance use disorders due to an increase in underlying patterns of corticolimbic abnormalities responsible for schizophrenic syndromes affecting the function of primary motivational circuitry, namely the mesolimbic dopaminergic system. **Financial support:** FAPESP, FADA, AFIP.

03.053

Antioxidant strategies revert aging-induced behavioral alterations in rats. Ricardo VP[1], Junior PRL[2], Batah PNE[2], Silva RCF[2], Frussa-Filho R[2] [1]UNIFESP/UNIP – Farmacologia/Ciências da Saúde, [2]UNIFESP - Farmacologia

Introduction: One of the major changes observed in the 20th century was the increase in the life expectancy of the human being. Aging can be seen as a consequence of a deficit of the homeostatic mechanisms, leading to the degeneration of the organism. The reason and the mechanisms related to these alterations are yet unknown. One of the main hypotheses suggests that aging derives from an imbalance between the production and the elimination of free radicals, or oxygen reactive species. It is well known that the central nervous system is also affected, although not to the same extent in all brain regions, promoting the surfacing of specific behavioral alterations. The aim of the present work was to investigate the effects of therapeutical strategies with antioxidant potential (food restriction and vitamins C+E administration) on aging-related behavioral alterations. **Methods:** 72 old rats (20 months) were used. The animals were allocated to four groups, which received a treatment with vitamins C+E (VICE), were submitted to 30% food restriction (FR30), received vitamins C+E treatment and were concomitantly submitted to 30% food restriction (VIFR), or none (NONE). Another group of 12 adult rats was used as control (CTRL). From sixty to ninety days later the animals were submitted to different behavioral evaluations: vacuous chewing movements quantification, open-field exploration/habituation, plus-maze discriminative avoidance task to evaluate learning/memory and anxiety, and step-through inhibitory avoidance. This work was approved by the Research Ethics Committee of São Paulo Federal University, number: 0459/07. **Results:** We verified that old rats presented an increase in the expression of orofacial movements (29.14 $\pm$ 3.59 and 14.3 $\pm$ 2.39 for NONE and CTRL groups, respectively), which was completely reverted by food restriction (16.54 $\pm$ 4.06 and 17.27 $\pm$ 1.99 for FR30 and VIFR groups, respectively) and attenuated by the administration of vitamins C+E (24.29 $\pm$ 5.33). We also observed that the locomotor deficit presented by old rats was also reverted by food restriction. Another behavioral alteration induced by the aging process which was reverted by the administration of vitamins C+E, and attenuated by food restriction, was the increase in the exploration of the open arms of the elevated plus maze discriminative avoidance apparatus. This last finding supports previous data, which demonstrated that both vitamin E and food restriction decreased the exploration of the open arms of a conventional elevated plus maze in adult rats. As concerns the cognitive impairments produced by aging, we observed that the treatment with the antioxidant vitamins and food restriction attenuated the learning/memory deficits in both elevated plus maze discriminative avoidance and step-through passive avoidance tasks, and also the habituation deficit in the open-field. **Discussion:** Based on the present results and supported by the current literature, one can conclude that the treatment with vitamins C+E and food restriction are highly beneficial interventions, attenuating or even reverting some of the major behavioral alterations developed by the aging process. **Financial Support:** FAPESP

03.054

Prevalência do uso de medicamentos em pós-graduandas com distúrbios do equilíbrio e/ou da audição. Salgado RS, Prezotto AO, Paulino CA, Onishi ET UNIBAN

Introdução: Os distúrbios do equilíbrio corporal e da audição (distúrbios vestibulares ou labirínticos) podem estar associados a vários fatores, incluindo reações adversas provocadas pelo uso de certos tipos de medicamentos. Alguns grupos farmacológicos são conhecidos por sua toxicidade sobre o labirinto, como os antiinflamatórios, diuréticos, moderadores de apetite, anticoncepcionais, alguns tipos de antibióticos, entre outros. Portanto, esse trabalho avaliou a prevalência do uso de medicamentos numa população de pós-graduandas com distúrbios do equilíbrio corporal e/ou da audição. **Métodos:** Foi estudada uma amostra de 123 mulheres, do município de São Paulo, com idades variando entre 20 (apenas 1 aluna) e 58 anos de idade, pós-graduandas em nível de *lato sensu*. As faixas etárias mais prevalentes foram as de 21 a 30 anos de idade (48%) e de 31 a 40 anos (27%), caracterizando uma população de mulheres adultas. O estudo foi do tipo transversal, descritivo, analítico, sem qualquer risco à saúde e integridade das participantes, sendo realizado nas dependências de uma Universidade Particular do município de São Paulo, após aprovação pela Comissão de Ética (Protocolo nº 174-07) e autorização da instituição. Para a coleta de dados foi elaborado e utilizado um questionário específico, com questões abertas e fechadas referentes a dados sócio-demográficos, de saúde, hábitos de vida e uso de medicamentos. Este instrumento foi previamente testado entre pós-graduandas adultas, voluntárias, as quais não participaram da amostra da pesquisa. **Resultados:** As queixas vestibulares mais relatadas pelas mulheres foram: cefaléia, dores musculares e cervicais, redução da concentração, redução da memória, tontura, redução da audição, náuseas, insônia, dificuldade de leitura, cinetose, zumbido e sudorese intensa. No tocante aos medicamentos, foi referido pelas pós-graduandas o uso de diferentes grupos farmacológicos e, muitas vezes, diferentes princípios ativos dentro do mesmo grupo. Excluindo o uso de anticoncepcionais (38%), e outros tipos de medicamentos, a prevalência dos grupos de medicamentos mais relatados foi: grupo dos analgésicos (70%), sendo 51% de analgésicos e antitérmicos, 12% de analgésicos e relaxantes musculares, e os demais analgésicos associados a outras propriedades; grupo dos antiinflamatórios (26%), sendo 20% de antiinflamatórios não-esteroidais e 6% de esteroidais; e grupo dos antialérgicos (13%). Ressalte-se que muitas pós-graduandas relataram o uso de mais de um medicamento. **Discussão:** A perda parcial ou total da função auditiva ou vestibular, durante ou após a exposição a medicamentos, entre outras substâncias, é chamada de ototoxicidade. Há muitas substâncias potencialmente ototóxicas (ou vestibulotóxicas), incluindo drogas com ação cardiovascular, psicotrópicos, relaxantes musculares, antiinflamatórios não-hormonais, antibióticos, hormônios, drogas para o aparelho respiratório, antialérgicos, drogas citostáticas, anestésicos, moderadores de apetite, e outros. O relato das pós-graduandas deste estudo sugere uma associação com o uso de alguns desses grupos medicamentosos e merece maior atenção farmacológica, pois esses medicamentos podem estar causando ou agravando as queixas relacionadas ao equilíbrio e/ou à audição. **Apoio financeiro:** UNIBAN.

03.055

Avaliação de anticolinesterásicos sobre aprendizado e memória de longa duração de camundongos. Pereira JD[1], Viel TA[2], Buck HS[3], Garcia AG[4], Caricati-Neto A[1], Jurkiewicz A[1], Jurkiewicz NH[1] [1]UNIFESP - Farmacologia, [2]EACH-USP [3]FCMSCSP - Ciências Fisiológicas, [4]UAM - Farmacologia

Introdução: O objetivo desse trabalho foi avaliar a atividade do composto 12118, um anticolinesterasico de síntese, no aprendizado de camundongos. O composto foi desenvolvido pelo grupo do Professor Antônio Garcia, da Universidade Autônoma de Madri. O composto possui estrutura híbrida, derivada da molécula do anticolinesterásico tacrina e da 1,4 diidropiridina nimodipina, inibidor de canal de cálcio do tipo L (Marco-Conteles et al., *J. Medic. Chem*. 49, 7607-7610, 2006). A síntese foi realizada para se obter fármacos mais potentes como candidatos para o tratamento da Doença de Alzheimer, utilizando a estratégia já existente de inibição de colinesterase, além da regulação dos níveis citoplasmáticos de cálcio, íon envolvido na patogênese da doença. **Métodos:** A metodologia tem como objetivo a análise do aprendizado e consolidação de memória de longa duração. Camundongos C57/Bl6 (20-25g, 4-5 meses de idade) foram tratados com 3mg/kg/i.p. de tacrina ou o composto 12118 e comparados ao grupo controle (salina em igual volume [2,5 ml/kg/i.p.]) 30 minutos antes de serem submetidos à avaliação da atividade locomotora por 5 minutos, em actômetro, onde foram registradas a deambulação e a exploração vertical. Em seguida, realizou-se uma sessão de treino em aparato de esquiva inibitória (0,5 mA, 2 seg, máximo de 300 seg) e dois testes para avaliação da memória de longa duração: 24 horas e sete dias após o treino. **Resultados:** Os animais tratados com salina e tacrina apresentaram aumento significativo da latência ao choque 24 horas (86,5seg [38,1/268,2] e 237,1seg [155,8/269,4], $P < 0,05$, respectivamente) após o treino (14,9 seg [7,0/30,4] e 23,9 seg [10,8/53,0]). Os animais tratados com 12118 apresentaram aumento ainda maior da memorização no teste realizado 24 horas (176,6 seg [101,5/228,0], $P < 0,01$) após o treino (20,0 seg [11,5/48,5]. Após sete dias, os animais de todos os grupos apresentaram aumento significativo da latência ao choque em relação à latência observada no dia do treino. **Discussão:** A injeção de fármacos antes da realização de uma tarefa tem o objetivo de se identificar uma possível ação dos mesmos no processo de aprendizado. Na concentração estudada, o aumento semelhante da latência ao choque para salina e tacrina em animais hígidos indica que nesses animais a tacrina não oferece vantagens. Por outro lado, a resposta aumentada do composto 12118 em animais sem déficit de memória sugere que em situações de disfunção da memória, esse composto poderia representar uma opção para a terapêutica de doenças neurológicas crônicas envolvendo déficit de memória. **Aprovado pelo CEP-UNIFESP:** Protocolo nº 1650/04. **Apoio Financeiro:** CAPES, CNPq e FAPESP

03.056

MDMA (*Ecstasy*) treatment alters leukocyte distribution by a glucocorticoid-dependent mechanism. Ferraz-de-Paula V[1], Ribeiro A[1], Hamasato EK[1], Moreau RLM[2], Palermo-Neto J[1] [1]FMVZ-USP – Patologia Veterinária, [2]FCF-USP - Análises Clínicas e Toxicológicas

Introduction: We have previously shown that MDMA (*Ecstasy*) changed the leukocyte distribution in blood, spleen and bone marrow. It has been reported that Ecstasy users are often more susceptible to infectious diseases, and a leukocyte distribution can be an important point in this issue. The aim of this study was to search for some mechanisms involved in the altered leukocyte distribution. **Methods**: The animals were housed and used in accordance with the guidelines of the Committee on the Care and Use of Laboratory Animal Resources of the School of Veterinary Medicine, University of São Paulo, Brazil, protocol: 1224/2007. Balb/C male mice were used and divided randomly 2 groups: Saline (C) and MDMA (10 mg/kg), 60 min after i.p. treatment blood, spleen e bone marrow samples were taken in order to evaluate the leukocyte distribution. **Results**: Previously to the treatment with MDMA or saline, mice received RU-486 (RU) (25mg/kg) or Propranolol (20mg/kg). We observed that the previously treatment with RU was able to prevent both reduction of cellularity (total number of cells x 10^6) in the bone marrow (C:78.13 ± 15.80; MDMA:49.11 ± 11.84; RU+MDMA:87.81 ± 15.14) and augmentation of cellularity in the spleen (C:199.4 ± 38.56; MDMA:289.7 ± 36.23; RU+MDMA: 225.1 ± 12.54), but RU was unable to prevent the effects of MDMA in the spleen relative weight. Additionally, Propranolol treatment was able to prevent only the effects of MDMA in the spleen relative weight (C: 0.39 ± 0.01;MDMA: 0.35 ± 0.006; Prop + MDMA: 0.42 ± 0.03), but not in the cellularity of bone marrow and spleen. **Conclusion**: Taken these data together, we showed that HPA axis activation and consequently corticosterone release were responsible for the altered leukocyte distribution and that cathecolamines are not involved. Therefore, we showed for the first time a neuroimmune-dependent mechanism for the actions of MDMA in the leukocyte distribution *in vivo*. Financial Support: FAPESP and CNPq.