adult male rats were implanted with microinjection cannulae into the accumbens nuclei (left and right), and48h later, they were injected with 1µl of saline or Na_2O_3Se(0.17 ng/L) into the left (ACC_L; n=10), right (ACC_R; n=15)or both neural structures (n=11) at 12:00h for three days. At four day, all animals were tested individually in a general motor activity detector (OVM) and in a Double Lateral Hole-Board Labyrinth (DHBL) to register general, motivated exploratory activity, and lateralized exploration induced by novelty. Results shown that in the OVM, stimulation of the ACC_R significantly inhibited head-dipping (5±1 Counts/5min Vs. 14.5±1 Counts/5min; Se Vs. Control,p <0.01) with no effect on rearingor focalized exploration. In the DHBL, general parameters of displacement and non-exploratory activity were not affected by treatments. However, lateralized exploration was inhibited when Se was injected into both ACC. In conclusion, results suggest that the ACC might be one possible site of action of trace elements, and evident lateralization was found in the ACC_R with on especific motivated exploration.

061 (110) **SE IS ABLE TO COUNTERACT THE INHIBITORY EFFECTS OF TE ON SELF-DEFENSE AND SOCIAL BEHAVIOURAL ACTIVITY IN THE RAT**

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Previously in our laboratory, evidence was presented showing that after systemic administration of Te in non-toxic doses to pregnant mother and its litter rats, several behavioural parameters related to motivated and lateralized exploration in the offspring were affected. Administration of systemic Se simultaneously with Te, blocked the inhibitory effect of Te on lateralized exploration, recovering the spontaneous left-biased exploration of animals in a double lateral hole-board labyrinth. In the present complementary work, the possible effect of Se on the inhibitory action that Te has on social and defensive behavioural activity, two important processes to the animal was studied. Four experimental groups were formed. Animals that received water (Control, n=10);animals that received ZnTe (0.03µg/L; n=10); animals that received Na2O3Se(0.268µg/L; n=10), and animals that received Na2O3Se +ZnTe (n=10). Treatments started with the pregnant mother and were continued along delivery, lactation and prepuberal stage of litter rats. At 30 day of age of the offspring, animals were tested individually in an intruder-resident(SIT), and a forced swimming test (FST) to measure social interaction and defense behaviour. Results in the SIT shown that, animals receiving ZnTe, latency to confront the intruder was significantly increased compared to control (131±36.5 Counts/3min Vs 13±3 Counts/3min, p<0.01). Animals receiving Se+Te showed a latency not different from Control and significantly lower than the ZnTe group (10±3 C/3min Vs 131±36.6C/3min; [Se+Te] Vs [Te], p<0.01. In the FST, ZnTe group showed a significant decrease in active swimming behaviour compared to Control; diminished activity that was blocked and restored to normal values in the (Se+Te) group. In conclusion, results show that social interaction and defensive behaviour, affected by the ZnTe treatment is restored to normal values by Se treatment.

062 (141) **DESIGN OF A LENTIVIRAL VECTOR AS A THERAPEUTIC STRATEGY AGAINST ALZHEIMER´S DISEASE**

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Alzheimer's disease (AD) is a chronic neurodegenerative disorder characterized by a progressive loss of cognitive functions. One of the hallmarks is the formation of amyloid plaques, composed mainly by Aß peptide oligomers (AβOs). Neprilysin (NEP) is the most important endopeptidase in charge of the degradation and clearance of Aß in the brain. Therefore, strategies aiming to increase NEP levels should contribute to decrease the amount of Aβ, AβOs and their deleterious effects on neurons, and could have a therapeutic effect. We are developing a lentiviral vector (LV), to deliver human NEP exclusively in hippocampal neurons. We will study its performance in vitro and in an AD transgenic rat model.

A construct containing the complete cDNA of NEP downstream of the hippocampal-specific promoter human synapsin (SYN-1) was developed. NEP cDNA was obtained from pBOB-NEP plasmid and was cloned under the SYN-1 promoter to obtain SYN-NEP plasmid. The correct cloning was checked by BamHI/KpnI digestion followed by 1% agarose gel electrophoresis. We obtained two bands of 3392pb and7644pb, which coincided with the molecular weight of NEP insert and plasmid backbone, respectively. The insert was also verified by sequencing. To test NEP expression by the plasmid, 293T cells were transfected with pSYN-NEP. pSYN-RFP plasmid expressing the reporter red fluorescent protein (RFP) and pBOB-NEP were used as transfection and positive controls, respectively. After 48 hours NEP expression was evaluated by western blot (WB) and RFP expression by fluorescence microscopy. Transfection efficiency was 80% and the WB showed a85kDa band only in those lanes corresponding to transfection with pBOB-NEP andSYN-NEP. In conclusion, NEP was successfully cloned downstream of SYN-1 promoter and is expressed correctly under a ubiquitous promoter. We are currently using this construction to produce LV for neuron-restricted expression of NEP.

063 (152) **ANGIOTENSIN II AT1 RECEPTORS MEDIATE NEURONAL SENSITIZATION AND THE SUSTAINED BLOOD PRESSOR RESPONSE INDUCED BY A SINGLE INJECTION OF AMPHETAMINE**

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A single exposure to amphetamine induces neurochemical sensitization in striatal areas. The neuropeptide angiotensin II, through AT_1 receptors (AT_1-R) activation, is involved in these responses. However, amphetamine-induced alterations can be extended to extra-striatal areas involved in blood pressure control and their physiological outcomes. Our aim for the present study was to analyze the possible role for AT_1-R in these events using a two-injection protocol and to further characterize the proposed AT_1-R antagonism protocol.

Central effect of orally administered AT_1-R blocker (Candesartan, 3mg/kg p.o. × 5 days) was analyzed recording spontaneus activity of neurons within locus coeruleus. In another group of animals, pretreated with AT_1-R blocker or vehicle, sensitization was achieved by a single administration of amphetamine (5mg/kg i.p.- day 6) followed by a 3week period off drug. After receiving an amphetamine challenge (0.5mg/kg i.p.),we evaluated: 1) the sensitized c-Fos expression in locus coeruleus (LC),nucleus of the solitary tract (NTS), caudal ventrolateral medulla (A1) and central amygdala (CeAmy); and 2) the blood pressor response. AT_1-Rblockade decreased LC neurons' spontaneous firing rate. Moreover, sensitizedc-Fos immunoreactivity was found in LC and NTS; and both responses were blunted by the AT_1-R blocker pretreatment. Meanwhile, no differences were found neither in CeAmy nor A1. Sensitized pressor response was observed as sustained changes in mean arterial pressure and was effectively prevented by AT_1-R blockade.

Our results support the important role for brain AT_1-R in amphetamine-inducedsensitization in extra-striatal areas and over its related cardiovascular output.

064 (153) **A SPECIFIC GLUCOCORTICOID RECEPTOR (GR) ANTAGONIST (CORT113176) PREVENTS INFLAMMATION AND NEURODEGENERATION IN THE WOBBLER MOUSE MODEL OF AMYOTROPHIC LATERAL SCLEROSIS**

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Wobbler (WR) mice show motoneuron degeneration, astrogliosis and microgliosis of the spinal cord. Additionally, increased plasma and brain corticosterone and focal adrenocortical hypertrophy suggest a role of hyperadrenocorticism in the WRdisease. In the present work we evaluated if antagonizing the GR with CORT113176prevents development of spinal cord abnormalities. CORT113176 shows high affinity towards GR without binding to progestin, androgen or estrogen receptors. Five month old genotyped WR mice received s.c. vehicle or 30 mg / kg / day for 4 days of CORT113176 dissolved in sesame oil. The mice were used the 4th day, 2 hours after the last dose of CORT113176. Antagonistnaïve WR showed several abnormalities of the spinal cord, such as vacuolated motoneurons, increased glial fibrillary acidic protein (GFAP) + astrocytes, decrease glutaminesynthetase (GS) + cells, increased number of IBA1+ microglia and decreased number of cells + for the calcium-binding protein B (S100B). Treatment of WR with CORT113176 normalized these altered parameters. Furthermore untreated WR expressed high levels of mRNA for CD11b (microglia marker) ($p < 0.01$ vs.control mice) and increased mRNA of proinflammatory markers TNa($p < 0.001$ vs. control) and iNOS ($p < 0.001$ vs.control). These markers were normalized in WR receiving CORT113176 (WRvs. WR CORT113176: CD11b: $p<0.05$; TNFa:$p<0.01$; iNOS: $p<0.001$). The TLR4 mRNA increased in the spinal cord of WR without treatment ($p < 0.01$ vs. control) and decreased with CORT113176 ($p<0.01$ vs. WR without treatment). In conclusion, the GR antagonist CORT113176 proved a powerful tool to block proinflammatory mediators, development of astrogliosis and microgliosis, thus holding back spinal cord neuropathology of WR mice.

065 (169) **PROTECTIVE ROLE OF LIPOIC ACID IN THE OXIDATIVE DAMAGE OF BRAIN STRUCTURES IN A GLAUCOMA RAT MODEL**

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Evidence of oxidative process was found in glaucoma brain so the use of an antioxidant therapy may hold a promise for treatment. The purpose was to evaluate the possible protective role of lipoic acid (LA) in the oxidative damage of geniculate nucleus (GN) and visual cortex (VC) in an experimental glaucoma model. Wistar rats (3 months) weredivided in four groups (n=20): glaucoma in which rats were operated under a microscope by cauterized two of the episcleral veins (G), glaucoma treated with LA 100 mg/kg i.p. (LG), control which received a sham procedure (C) and control treated with lipoic acid 100 mg/kgi.p. (LC). Seven days after surgery rats were euthanized, brains were removed and GN and VC were separated. The following markers were evaluated:thioredoxin reductase (TRxR), glutathione reductase (GR) and superoxidedismutase (SOD) activities, protein oxidation (PO), damage to lipids (TBARS) and glutathione (GSH).

Comparing LA treated glaucoma to glaucoma: TRxR increased 52% in GN (G 7.6±0.4 nmol/min.mg protein *p<0.01*) and 26% in VC (G 9.9±1.0 nmol/min.mg protein *p<0.05*), GR increased 82% in GN (G 8.2±1.2nmol/min.mg protein *p<0.01*) and 300%in VC (G:5.1±1.3 nmol/min.mg protein *p<0.001*),SOD increased 23% in GN (G 18.0±1.1 U/mg protein *p<0.05*) and 80% in VC (G 6.0±0.4 U/mgprotein *p<0.001*), PO diminished 52%in GN (G 22.9±2.3 nmol/mg protein *p<0.05*)and 58% in VC (G 9.34±1.30 nmol/mg protein *p<0.05*),TBARS diminished 25% in GN (G 4.8±0.4 nmol/mg protein *p<0.05*) and 36% in VC (G 5.3±0.6 nmol/mg protein *p<0.05*), GSH increased 42% (G 0.20±0.04µmol/g *p<0.05*) in GN and 73% (G 0.41±0.03µmol/g *p<0.01*) in VC.

The increase in GSH and in the activities of antioxidant enzymes could have been a consequence of the protective role of LA in oxidative processes in glaucoma. Furthermore, the protective effect against lipid and protein damage and the improvement inGSH recycling support that LA could be used as a novel therapy for reducing oxidative damage in glaucoma.

066 (189) **KISSPEPTIN PARTICIPATION IN DELETERIOUS GHRELIN EFFECTS ON SPERMATOGENESIS**

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Physiological mechanisms that control energy balance are reciprocally related to those that control reproductive function. In previous work we have shown that chronic intrahypothalamic ghrelin(Ghr) administration (42 days), an orexigenic peptide of 28 amino acids, decreases epididymal sperm concentration and motility in mice, these results correlate with a reduction in plasma testosterone concentration.

In this study, we investigated the involvement of kisspeptin (Kiss-1) system and its receptor (GPR54) in deleterious effects on spermatogenesis after chronic Ghr central administration. Albino Swiss adult male mice were implanted with osmotic pumps (Alzet) Model 1007D (0.5 l / hour-7 days) ormodel 2006 (0.15 l / hour-42 days) on hypothalamus and infused with sterile cerebrospinal fluid (CSF-control) or different Ghr doses (0.3 or 3.0 nmol /ul). Animals were sacrificed and the hypothalamus dissected to assess the expression of genes encoding gonadotropin releasing hormone (GnRH), Ghr receptor (GHRS), Kiss-1 and GPR54 by real time PCR.

Results show a significant decrease of relative Kiss-1 expression ($F = 10.25$, $p \leq 0.05$) and its receptor GPR54 ($F = 11.34$, $p \leq 0.05$) in animals treated per 7 days with Ghr 3,0 nmol/ul, while peptide administration for 42 days only decreases GPR54 expression ($F = 9.03$; $p \leq 0.05$). No significant differences were found in GHRS or GnRH expression ($p > 0.05$).

This paper provides new evidence about possible mediators involved in Ghr deleterious effect on male reproductive system, indicating that this peptide induces a negative modulation at central level on the expression of Kiss-1 and / or its receptor.

067 (400) **EFFECTS OF EARLY LIFE STRESS ON NEUROGENIC BRAIN REGIONS: ACTIVITY OF LINE-1 RETROTRANSPOSONS DECREASES IN HIPPOCAMPAL NEURONS IN RATS SUBJECTED TO NEONATAL-MATERNAL SEPARATION.**

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Long Interspersed Nuclear Elements-1 (LINE-1) retrotransposons are repetitive elements that encode an RNA binding protein (ORF1p)and an endonuclease with reverse transcriptase activity (ORF2p), that control LINE-1mobilization via target prime reverse transcription. Despite most human LINE-1insertions occur during early embryonic development, somatic retrotransposition also takes