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"DETERMINANTS OF ALCOHOLISM: BRIDGING THE GAP BETWEEN EPIDEMIOLOGICAL AND BASIC RESEARCH"

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KEYNOTE CONFERENCES

INTERVENTIONS FOR FETAL ALCOHOL SPECTRUM DISORDERS: FROM THE LAB TO THE CLINIC

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Prenatal alcohol exposure disrupts brain and behavioral development, leading to a range of fetal alcohol spectrum disorders (FASD) that include long-lasting deficits in cognitive functioning. Unfortunately, fetal alcohol spectrum disorders constitute a serious global health problem, as women continue to drink during pregnancy. Thus, it is critical to identify treatments to improve outcome among individuals exposed to alcohol prenatally. Research suggests a number of strategies can be taken, from blocking alcohol's teratogenic actions to treating specific symptoms. Identification of factors, such as nutrition, that modify ethanol's teratogenic effects can also lead to novel means to reduce FASD. Using an animal model, we have shown that supplementation with the nutrient choline can attenuate ethanol's damaging effects on the fetus. In fact, choline can even reduce the severity of FASD when administered postnatally, after a prenatal alcohol insult. When administered postnatally, choline attenuates ethanol's effects on hippocampal development and can improve performance on cognitive tasks that depend on the functional integrity of the hippocampus. Choline likely acts through multiple mechanisms, serving as a precursor to the neurotransmitter acetylcholine, a precursor to cell membrane constituents, and a methyl donor. Thus, choline can influence synaptic neurotransmission, cell signaling, and epigenetic regulation. Recent data also indicate that early choline supplementation can lead to long-lasting enhancements in neuronal plasticity, evident long after choline treatment has ceased. Importantly, several current clinical trials show promising results of choline supplementation reducing FASD, suggesting that this treatment may translate to clinical populations. Ultimately, identification of safe and effective treatments that are easily translated to clinical populations are critically important for improving the quality of life of individuals with FASD.

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THE FUTURE OF SOCIAL NORMS: REVOLUTIONIZING NORMATIVE FEEDBACK INTERVENTION VIA GAMIFICATION

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Heavy drinking among emerging adults and college students remains a grave health risk resulting in serious and costly consequences. Further, students overestimate how much and how often other students drink, and these normative perceptions are among the strongest predictors of their own drinking levels. Personalized normative feedback (PNF), which corrects these misperceptions, has been shown to be consistently effective at reducing normative beliefs and drinking. However, these effects have been modest and the research has seemed to plateau due to limitations such as reactance, lack of credibility, lack of personal relevance,

and forced participation. This presentation represents a developing research agenda to innovatively address these limitations. First, we attempted to deliver PNF live with in-tact groups using polling. In our study, the norms were created by peers in the moment (reducing reactance), statistics were immediately displayed (increasing credibility), and rather than national or campus-wide data, the results were specific to a group that the student belonged to (increasing personal relevance). Norms reduced immediately after participation and drinking behavior was reduced at the 1 and 2 month follow ups for groups of Greek life members, college athletes, and first-year students. Next, in order to extend this work's reach, we used the growing gamification literature to develop an online social-media infused social norming game and tested isolated features of this approach. A pilot study of first-year college students tested a gamified social-media based app created to deliver alcohol-related PNF. Three-hundred fifty students voluntarily played the game weekly for six weeks during their first semester in college and were randomized to receive alcohol feedback or no alcohol feedback. Results revealed that participants shown alcohol feedback, especially those who were heavy drinkers before taking place in the intervention, reduced their drinking significantly during the two month post-intervention, relative to control participants. Further alcohol feedback combined with reflective judgment feedback (feedback on what opposite sex peers felt about the behavior) was particularly effective and had effect sizes 2-3 times greater than typical PNF interventions. These findings suggest that gamified normative interventions have the potential to be self-sustaining and highly effective. Further, we report on a series of studies that isolated features of gamification used in the pilot and examined their effectiveness. First, results showed that when question topics and feedback topics were chosen by chance (via slot-machine spinners), students' reactance to the feedback material decreased, and they had larger reductions in drinking. Then we explored the role of virtual copresence (the experience of seeing peers who are participating in the formation of peer norms via profiles) and found greater levels of copresence led to the greater reductions in drinking via increasing the believability and salience of the feedback data. In the end, gamified social norms interventions which incorporate user-generated questions, slot machine-style spinners, user profiles, points, and wagering on answers, is an innovative shift in the delivery of PNF that may improve their effectiveness and change the way PNF is conducted.

ENVIRONMENTAL ENRICHMENT: AN OVERVIEW ON STRESS AND ALCOHOL INTAKE

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Environmental conditions have a major influence on the drug-induced behavioral and neurochemical effects. Stress has an important role in the development of addiction as well as relapses. On the other hand, exposure of rodents to toys, exercise wheels and social stimuli, a model known as environmental enrichment (EE), is capable of producing beneficial effects to the individual and preventing or reversing pathological conditions, including behavioral / neurochemical effects induced by drugs of abuse. Data from our laboratory demonstrated the involvement of BDNF (Brain-Derived Neurotrophic Factor) in the prefrontal cortex of animals submitted to EE, suggesting a possible role of this neurotrophic factor in the EE-induced neurochemical mechanisms (Rueda et al., 2012; Pautassi et al., 2017). Several molecules are commonly involved in neuroadaptation signaling induced by stress and dependence, such as the corticotropin release factor (CRF) and the BDNF. This study aimed to evaluate the involvement of EE-induced epigenetic modifications in the

Bdnf gene of enriched mice exposed to chronic unpredictable stress. The results suggest that enrichment is capable of altering the Bdnf expression. Chronic stress interferes with the protective effect of EE revealing an anxiogenic phenotype, which is reversed by metyrapone, in circumstances of high plasma corticosterone concentrations. Financial support: FAPESP, CNPq

SYNERGY OF ANTIINFLAMMATORY AND ANTIOXIDANT AGENTS REDUCES CHRONIC ALCOHOL INTAKE AND PREVENTS RELAPSE BINGING IN PRECLINICAL STUDIES.

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Chronic voluntary alcohol consumption in a Wistar-derived alcohol-preferring rat (UChB) leads to intakes exceeding 10 g ethanol/kg/day. Hippocampi of these animals show 200% increases in oxidative stress determined as the ratio of oxidized/reduced glutathione (GSSG/GSH), neuroinflammation determined by 30-60% increases in astrocyte glial-fibrillary acidic protein (GFAP) and similar increases in microglial density (Iba-1). Noteworthy, these changes remain long after ethanol intake is discontinued; indicating the existence of a self-perpetuation (*vicious cycle*) of oxidative stress and neuroinflammation. Which of these arises first is not clear, but both activate the NF-kB system promoting and maintaining neuroinflammation. Administration of the antioxidant N-acetyl cysteine (40-100 mg/kg) fully reverses brain oxidative stress and neuroinflammation and inhibits chronic alcohol intake by 70%. Following chronic ethanol intake, N-acetyl cysteine administered to animals during a 2-week alcohol deprivation period blocks neuroinflammation and oxidative stress and inhibits by 60-70% the relapse binge-like drinking ("ADE") prompted by the subsequent ethanol re-access. Studies also show that aspirin an anti-inflammatory drug available "over-the-counter" blocks the neuroinflammation-oxidative stress cycle and synergizes the inhibitory effects of N-acetyl cysteine both on chronic ethanol intake and relapse binge-drinking. The combination of N-acetyl cysteine + aspirin inhibits by 85% ethanol intake relapse (ADE). Mesenchymal stem cells (MSC) and MSC-products known for their marked anti-inflammatory and antioxidant properties also strongly inhibit chronic ethanol intake and relapse binge-drinking drinking. These studies further show that MSCs and aspirin normalize the ethanol-reduced levels of the glial glutamate transporter GLT-1. N-acetylcysteine is known to increase the xCT cystine/glutamate transporter. Overall, studies tie neuroinflammation-oxidative-stress and hyper-glutamatergic conditions as the likely mechanism that perpetuate chronic alcohol intake and promotes intoxicating relapse drinking. Studies suggest that clinical trials of presently available antioxidant and anti-inflammatory agents may add significantly to interventions aimed at reducing alcohol-use disorders.

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GENE X ENVIRONMENT INTERACTIONS IN ALCOHOLISM: FOCUS ON PRODYNORPHIN GENE

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The roots of alcoholism have been linked to either environment or heredity, however how alcohol exposure, environmental stress and heritable factors interact is still largely unexplored. Recently, molecular research has created a foundation for understanding how these factors may interact to facilitate disease progression and exposure to alcohol activating epigenetic mechanisms. Among others possible targets, we here focus the attention on dynorphins already found to be critically involved in the development, maintenance and relapse of alcoholism. We show how alcohol-induced changes in the prodynorphin gene expression may be influenced by both gene polymorphisms and epigenetic modifications analyzing (1) DNA methylation patterns in the prodynorphin gene promoter (2) prodynorphin single nucleotide polymorphisms associated with alcohol dependence in genomic DNA isolated from peripheral blood cells of alcoholics and healthy controls. Moreover, using a rat model of Prenatal Alcohol Exposure, we report the transcriptional regulation of prodynorphin gene in selective brain regions and how an environment switch modifies it, as well as the anxiety-prone phenotype evoked by alcohol exposure. There is an urgent need for biomarkers in psychiatric disorders, including alcoholism, and the understanding of gene-environment interactions is extremely important in the attempt to develop new treatments such as epi-treating factors and/or drugs targeting the prodynorphin gene.

A MOUSE MODEL OF REPEATED ALCOHOL EXPOSURE AND WITHDRAWAL TO EVALUATE MEDICATIONS TO TREAT EXCESSIVE ALCOHOL CONSUMPTION

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Alcoholism is characterized as a chronic relapsing disease and relapse prevention represents a major challenge to treatment efforts. Unfortunately, despite significant progress in our understanding of biological and environmental factors that drive excessive alcohol consumption, there are few treatments available to help those suffering this disease. The development of animal models has been very valuable in the advance of our knowledge of biological and environmental factors that modulate excessive drinking. These models have also been instrumental in the development of pharmacological tools that can help reduce excessive drinking and/or prevent relapse. This presentation centers on the development of a mouse model that combines voluntary alcohol (ethanol) intake with a protocol of alcohol exposure that produces dependence. Chronic intermittent ethanol (CIE) exposure results in a significant increase in voluntary ethanol intake compared to control, non-dependent mice. CIE exposure also promotes tolerance to the aversive effects of ethanol and insensitivity to the devaluation of ethanol reward. The translational potential of this model has been explored using drugs already approved to treat alcoholism such as topiramate, naltrexone, and disulfiram.

These drugs efficiently reduced voluntary ethanol intake, especially in CIE exposed mice. Other known compounds such as doxazosin (alpha1 adrenoreceptor antagonist) and mifepristone (glucocorticoid receptor antagonist) can also reduce voluntary ethanol intake in ethanol dependent and non-dependent mice. This model has also been used to evaluate compounds that are still under development to treat alcohol abuse. A summary of the effect of these compounds on voluntary ethanol intake will be presented to highlight the use of this preclinical model that can help screen and identify promising pharmacological agents. Results obtained with this model could promote clinical investigations regarding the treatment of excessive drinking in the context of alcohol dependence.

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SYMPOSIUM

ROLE OF ETHANOL METABOLITES IN ALCOHOL ABUSE AND DEPENDENCE

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Ethanol in the brain is oxidized by catalase to acetaldehyde, which is subsequently eliminated by aldehyde dehydrogenase. Despite its peripheral aversive effects, studies in rats have shown that acetaldehyde displays rewarding effects at central level, since it is self-administered intracerebrally at micromolar concentrations, suggesting that acetaldehyde would be the active effector of ethanol. Acetaldehyde can condense with dopamine in the brain to form salsolinol, a potent reinforcing compound. Animal studies show that salsolinol administration can sensitize animals for ethanol drinking. This effect of salsolinol is blocked by the administration of opioid antagonists, which agrees with in vitro studies showing that salsolinol is an agonist of the mu-opioid receptor. By inhibiting the production of acetaldehyde in the ventral tegmental area (VTA) by stereotaxic injection of a lentiviral vector encoding an anti-catalase shRNA or accelerating its degradation by injection of a vector overexpressing aldehyde dehydrogenase, we observed an inhibition of 95% in the voluntary alcohol consumption in UChB high-drinking rats, and an inhibition of ethanol-induced dopamine release in the nucleus accumbens. Overall, these data support the hypothesis that acetaldehyde generated by catalase in the brain produces reinforcing effects, most likely combining with dopamine to generate salsolinol, which binds and activates opioid receptors, and ultimately generating a disinhibition of dopaminergic neurons present in the limbic reward system.

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MALE AND FEMALE REPRODUCTIVE EFFECTS ON GONADS, GERM CELLS AND EARLY EMBRYOS PRODUCED BY PARENTAL ALCOHOL INGESTION, IN THE MOUSE MODEL.

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Chronic alcohol consumption affects the male and female hypothalamic-pituitary-gonadal axis. However, the effects of moderate-low alcohol intake at gonadal-germinal level and its impact on early embryonic development have not been fully described. Previously, we demonstrated in mouse that chronic administration of 5-10% alcohol in drinking water, decreases the ovulation, alters the oocyte quality and reduces the fertilization rate (IVF); while in the male, only the moderate alcohol concentration (10%) induced teratozoospermia, without changes in the sperm functionality and fertilization. However, paternal 10% alcohol consumption

induced delayed preimplantation development from day 3 to 7 of culture, whereas the administration of alcohol 5% to murine females affected the development from the postzygotic stages. Recently, we focused on the gonad-germinal impact of moderate semichronic intake (15 days) of alcohol (10, 15%) in the mouse (Blood alcohol concentration: 15–60 mg/dL, ethanol consumption: 18-30 g/kg/day, 24-30 % EDC). In 80% of females treated with 10% alcohol, the cyclicity was altered, evidenced by permanent diestrus and lower estrus frequency. After intake, the number of preantral-antral follicles was significantly reduced compared to controls. Although ovulatory induction (5 IU eCG/hCG) restores folliculogenesis, high spontaneous parthenogenetic activation and increased frequency of oocytes with abnormal metaphase II remained observed. After semichronic alcohol administration, the testicular seminiferous tubules had reduced epithelial diameter, disorganization, vacuolization, apoptosis and altered intercellular adhesion. In addition, we recently demonstrated that, although the acrosomal reaction and hyperactivation of motility decreased after semichronic treatment, during IVF timing (2.5, 3.5 and 4.5 h) increased percentages of fertilized oocytes, of *in vitro* induced-decondensed sperm heads and sperm morphologically abnormalities were observed. These results suggest that short-term moderate alcohol consumption in male and female mice affects the fertility and may potentially lead to ulterior early embryonic development impairment, hypothesis that now are under studying.

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BREATHING RESPONSES IN ETHANOL-EXPOSED FETUSES

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The anatomo-physiological disruptions inherent to different categories of the Fetal Alcohol Spectrum Disorder do not completely encompass all the negative consequences derived from intrauterine ethanol (EtOH) exposure. Preclinical, clinical and epidemiological studies clearly show that prenatal EtOH exposure also results in early programming of alcohol affinity. This affinity has been primarily addressed through the examination of how EtOH prenatally exposed organisms recognize and prefer the drug´s chemosensory cues, their predisposition to exhibit heightened voluntary EtOH intake during infancy and adolescence and the presence of seeking behaviors of EtOH´s reinforcing effects. In altricial species these processes are determined by the interaction of at least three factors during stages equivalent to the 2nd and 3rd human gestational trimester: i) fetal processing of the drug's olfactory and gustatory attributes present in the amniotic fluid ii) EtOH's recruitment of central appetitive motivational mechanisms that also imply progressive sensitization to the drug's reinforcing effects and iii) an associative learning process involving the prior two factors. This pavlovian learning phenomenon is highly dependent upon the recruitment of the opioid system and recent studies also indicate a significant role of EtOH's principal metabolite (acetaldehyde, ACD) which is rapidly generated in the brain via the catalase system. The central and rapid accumulation of this metabolite in the developing organism represents a major factor involved in the process of fetal alcohol programming. According to recent investigations it appears that ACD not only exerts early positive reinforcing consequences but also antianxiety effects (negative reinforcement). These recent experimental approaches also suggest that relatively few episodes of early EtOH intoxication are sufficient to induce a conditioned activity of the central catalase system; particularly when the organism is treated and tested under stressful conditions. Finally, this

review also acknowledges human clinical studies indicating that moderate and binge-like drinking episodes during gestation result in neonatal recognition of EtOH´s chemosensory properties coupled with preference towards these cues which additionally trigger respiratory plasticity alterations that endanger the well-being of the newborn. As a whole, the studies under discussion emphasize the notion that even subteratogenic EtOH exposure during fetal life seizes early functional sensory and learning capabilities that pathologically shape subsequent physiological and behavioral reactivity towards the drug.

ADVANCES ON THE EFFECTS OF ENVIRONMENTAL ENRICHMENT ON ALCOHOL INTAKE AND REWARD IN ANIMAL MODELS

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Environmental enrichment (EE) has been used as a non-pharmacological tool to reduce anxiety-like behaviors induced by stressors. In our laboratory, we have found that EE can attenuate relevant processes related to addiction, like ethanol behavioral sensitization and stress-induced ethanol intake. The beneficial effects of EE on stress-induced alcohol intake has been demonstrated after restraint stress or a psychological stressor. We have also found that EE increases ethanol-induced rewarding effects, evaluated by the conditioned place preference paradigm. This effect is mediated via oxytocinergic mechanism, which may involve increases in D1 receptor levels in the nucleus accumbens.

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ALCOHOL'S EFFECTS IN WOMEN WHO UNDERWENT BARIATRIC SURGERY

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Bariatric surgery procedures provide the most successful long-term treatment for severe obesity. Currently, the three most popular bariatric surgeries performed worldwide are the Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), and laparoscopy adjustable gastric banding (LAGB). All three procedures decrease gastric volume, but unlike LAGB, in which the stomach/intestine remain intact, both SG and RYGB alter stomach anatomy and RYGB also reroutes the intestine. Despite the numerous health benefits of these procedures, there is an increased risk to develop an alcohol use disorders (AUD) after this stomach surgeries. The precise mechanism(s) underlying such increase risk for AUD is uncertain, but we hypothesize it is due to gastric resection surgery-induced changes in both: 1) alcohol pharmacokinetics and 2) gut-brain peptides, which modify brain pathways that play a role in food and alcohol reward (e.g., ghrelin, glucagon-like peptide 1). I will review epidemiological findings supporting an increased risk of AUD after these surgeries, and will present data of an ongoing study in which we are evaluating the effects of RYGB, SG or LAGB surgery on the pharmacokinetics and subjective effects of ingesting ~ two standard drinks. Our data, combined with

data from others, underscore the need to make patients aware of the alterations in alcohol metabolism that occur after these bariatric surgery procedures to help reduce the risk of potential serious consequences of moderate alcohol consumption.

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SALE AND PROBLEMATIC CONSUMPTION OF DRUGS

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According to studies conducted by the Observatory of Argentine Social Debt (2017), alcohol consumption and the perception of drug sale have increased in recent years among young adults. The present study is based on the answers given to a survey by young adults (15 to 29 years old) from three different urban areas of Argentina: the City of Buenos Aires, the Province of Santa Fe, and the slums and informal settlements of the Conurbano Bonaerense. The data was collected in 2015, the interviewees were selected through a random and multistage sampling with gender and age quota. Data showed that nine out of ten young adults have consumed alcohol at least once in their lives, 90% of whom started drinking before they were eighteen years old. 60% of the respondents consumed alcoholic beverages in the last thirty days, 25% of whom got drunk. Moreover, two out of ten young adults showed an alcohol abuse behavior, and considered that they drink quite a lot. Alcohol consumption frequency increases with age, and is more prevalent among men and lower socio-economic statuses. On the other hand, alcohol was found to be the gateway to the consumption of other substances. Associated consumption is high among young people. Marihuana is the most widely used illegal substance among young adults, and its consumption is usually perceived as less harmful than the use of other drugs. Illegal substance consumption is not exclusive to any social-economic status. However, the conditions presented by the most vulnerable socio-residential environment are associated with an increase in drug sale and accessibility to illegal substances.

IMPACT OF LEAD EXPOSURE ON ETHANOL METABOLISM: *IN VITRO* AND *IN VIVO* APPROACHES

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Early-life exposure to lead (Pb) induces neurobehavioral alterations in living organisms, including an altered response to drugs. We have reported a higher voluntary ethanol intake followed by hyperactivity in perinatally-Pb-exposed rats. Ethanol oxidation to acetaldehyde is catalyzed by the enzyme alcohol dehydrogenase (ADH) in the liver and by catalase (CAT) in the brain, while the final oxidation to acetate is mediated by mitochondrial aldehyde dehydrogenase (ALDH2). Taking into account this two-compartment model in

rodents, several authors assign positive reinforcing properties to brain-generated acetaldehyde. In effect, pharmacological o molecular inhibition of CAT decrease, while CAT pharmacological activation or brain ALDH2 inhibition increased voluntary ethanol intake in the Pb-exposed rats. These results are complemented with data obtained in the nematode *Caenorhabditis elegans* in a similar model of perinatal Pb exposure. Ethanol-induced locomotor activity evaluated in wild type strains revealed a higher tolerance to the sedative properties of ethanol in the Pb-exposed animals, an effect that was prevented when ADH mutants were evaluated. Further studies indicated a lower functionality of ADH as a result of perinatal Pb exposure, pointing out the importance of the non-metabolized ethanol fraction in this model. On the other side, our studies in the SH-SY5Y cells concomitantly exposed to Pb and ethanol evidenced a decrease in ALDH activity, which is restored by Alda-1, an ALDH activator or by NAD^+ supplementation, the cofactor of this enzyme. Overall, these data revealed the relevance of an adequate functionality of ethanol metabolizing enzymes in the stimulant and motivational effects of the drug, and how this process is impacted by early exposure to Pb, an environmentally-relevant neurotoxicant.

POSTERS

ALDH2 ACTIVITY IS DECREASED BY ETHANOL AND LEAD EXPOSURE: RECOVERY BY NAD+ AND ALDA-1 IN NEUROBLASTOMA SHSY-5Y CELLS.

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Clinical and experimental evidences in laboratory animals demonstrate that the neurotoxicant lead (Pb) induces neurobehavioral alterations, including an altered response to drugs. We have previously reported that perinatally-Pb-exposed rats showed elevated ethanol (EtOH) intake, which seems to be mediated by brain acetaldehyde (ACD) accumulation. Thus, based on a reduced brain mitochondrial ALDH (ALDH2) activity and expression observed in the Pb-exposed rats, *in vitro* experiments were performed in neuroblastoma SH-SY5Y cells, aimed to modulate ALDH2 activity in a brain like-environment. ALDH2 functionality depends on nicotinamide adenine dinucleotide (NAD +) availability, its cofactor which is generated within the mitochondria. Interestingly, activators such as Alda-1 were used to restore ALDH activity as a therapeutic strategy, not only in alcohol-related disorders but also in several brain conditions. Thus, neuroblastoma cells were exposed to Pb (5-200μM), EtOH (100-200 mM) or Pb plus EtOH (10μM/200mM) for 24 h. Moreover, NAD + (1mM) and Alda-1 (20 μM) were used as therapeutic strategies to enhance ALDH2 activity in all groups. The results resembled the *in vivo* data showing that Pb alone (5μM and 10μM), EtOH alone (100-200 mM) and their combination inhibited ALDH2 activity in SH-SY5Y cells. Concomitant supplementation with NAD + increased the enzyme activity in all groups (except the controls), suggesting either a reduction in NAD + bioavailability or an altered affinity of the enzyme for its cofactor resultant of the combined neurotoxic effects of Pb and EtOH in these cells. Interestingly, Alda-1 treatment restored the enzyme activity in a higher ratio, suggesting a different mechanism of activation, probably related to its proposed protective role in ALDH2 inactivation by adduct formation of the enzyme and toxic bioproducts. Future experiments will be focused on the study of these activators in an *in vivo* model to evaluate their effects on the reported elevated EtOH consumption observed in the Pb-exposed rats. Funded by: MinCyT, CONICET and SeCyT-UNC, Argentina.

THREE IMPULSIVITY CONCEPTS, ALCOHOL AND NEUROCOGNITIVE PROFILES

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Impulsivity has been described as both a personality factor that may promote greater alcohol consumption. Therefore, it is interesting to inquire about the different dimensions of Impulsivity. A tripartite perspective of Impulsivity will be developed here, with the underlying assumption that, Compulsive Urgency, Impulsivity by Improvidence and Sensation Seeking, are necessary to understand the complexity of this construct. We investigated whether a self-report test of three types of impulsivity could be a good predictor of cognitive functioning in healthy individuals. The sample was composed of 180 subjects (60% women) with a mean age of 27.3 years (*SD* = 12.6 years) from the general population of the Autonomous City of Buenos Aires, Argentina. The sample was evaluated using the Questionnaire on Compulsive Urgency, Sensation Seeking, and Impulsive Improvidence (CUBI-18; Squillace Louhau, & Picón Janerio, 2019). A battery of neuropsychological tests was administered to measure executive-attentional functioning, verbal and non-verbal fluency, speed of processing, and decision-making process. A report of the family provided information on risky behaviors. Results showed a differential profile of the three subtypes of impulsivity. Compulsive Urgency was associated with greater executive- attentional difficulties, Impulsive Improvidence with lower fluency in processing nonverbal information, as well as with greater occurrence of risk behaviors in everyday life (as indicated by family reports), including greater engagement in alcohol. The present results are relevant to understand the different dimensions of impulsivity and their relation with several behaviors, including alcohol use.

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ETHANOL-RELATED LEARNING IN RAT NEONATES IMPACT UPON APNEIC EPISODES AND PROMOTE SEEKING BEHAVIOR OF STIMULI THAT SIGNALED THE STATE OF INTOXICATION

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In rats, high ethanol doses during early postnatal life exert deleterious effects upon brain development that impact on social and cognitive abilities. This stage in development partially overlaps with the 3rd human gestational trimester in terms of synaptogenesis. At this stage, human fetuses and rat neonates (postnatal days, PDs 3-9) exhibit relatively high respiratory rates that are affected by subteratogenic ethanol doses. Recent studies suggest conditioned breathing responses in the developing organism given explicit associations between exteroceptive stimuli and the state of EtOH intoxication. The present study was meant to analyze how apneic episodes are affected by the drug itself or through learning processes involving this psychotropic agent. During PDs 3, 5, 7 and 9 rats were subjected to differential experiences with salient tactile cues explicitly paired or not with the effects of vehicle or EtOH (2.0 g/kg) intragastric administration. A tactile discrimination paradigm applied during PDs 3, 5, 7 and 9 was conducted under stressful circumstances (maternal deprivation, exposure to a novel environment and drug administration procedure) for the developing organism. Pups were individually tested in a whole body plethysmograph where a given tactile cue was presented under the state of sobriety while an alternative texture was associated with the state of intoxication. Ethanol intoxication systematically inhibited the occurrence of apneic episodes. Most importantly, it was observed that tactile cues (either smooth or rough) systematically paired with ethanol intoxication also promoted inhibitory effects upon the emergence of apneas (isodirectional conditioned response). The study also revealed that ethanol also results in a sensitization process relative to its inhibitory effects upon apneic episodes. At PD11, pups were tested in a two-way tactile preference test defined by the textures previously experienced. This test revealed that ethanol intoxication increased preferences towards the stimuli that predicted such a toxic state. These last results may imply both the systematically reported positive reinforcing effects of ethanol during early ontogeny and/or its negative reinforcement capability in terms of antianxiety effects. As a whole these results emphasize the need to consider ethanol's motivational effects during early development upon the regulation of breathing patterns and subsequent affinity for the drug.

GLIAL CELL RESPONSE TO IRON DEFICIENCY AND ALCOHOL CO-EXISTENCE

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Nutritional iron deficiency (ID) negatively affects central nervous system (CNS) since the pregnancy until early adolescence, and also potentiates alcohol effects on CNS through cellular mechanisms that are poorly known. Our hypothesis proposes that co-existence of ID and alcohol affects glial cells, predominantly astrocytes, causing a deleterious response that is clue to the perpetuation of CNS damage. To validate this postulate, we analyzed the effects of ID and alcohol by exposing neonatal cortical astrocytes to the iron chelator desferoxamine (DFO, 25 mM) during 96 h and then to ethanol (EtOH, 100 mM), mimicking a single high alcohol exposure upon sustained ID. After 24 h of EtOH incubation, parameters associated to the astrocyte response were assessed, including expression of prototypic markers, mitochondrial potential and functionality (evaluated by JC1 and MTT), oxidative stress levels (estimated with dichlorofluorescein and monochlorobimane) and endoplasmic reticulum (ER) stress analyzed by BiP/GRP78immunolabelling. Morphology and survival of hippocampal neurons co-cultured on astrocytes of all experimental conditions were also studied. Results obtained on astrocytes indicate that EtOH worsen the parameters associated with oxidative and ER stress, that DFO did not cause significant effects and that DFO-EtOH condition caused a significant decrease in mitochondrial potential and functionality as well as decreased levels of glutathione. Survival of neurons that were co-cultured on astrocytes of DFO-EtOH condition decreased ~ 20% whereas in EtOH condition and DFO only showed a tendency to decrease. Thus, simultaneous presence of DH and alcohol alters the astrocyte phenotype affecting neuronal survival to a greater extent than each condition separately. Therefore, astrocytes seem to be involved in the damage caused by DH and alcohol on the CNS and could be a potential therapeutic target.

DISRUPTIONS OF SEROTONERGIC TRANSMISSION DURING SENSITIVE DEVELOPMENTAL PERIODS RESULTS IN ELEVATED ALCOHOL INTAKE AND ALTERED ANXIETY-RELATED BEHAVIOR.

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Serotonin (5-HT) is a monoamine neuromodulator that is involved in the regulation of numerous physiological and behavioral functions including mood and anxiety related behaviors. 5-HT is also involved in refining the formation of brain circuits during sensitive developmental periods. It is not surprising, though, that 5-HT plays an important role in the development of psychiatric disorders such as social deficits, anxiety, depression and addiction problems. It is known that anxiety disorders have developmental origins and that 5-HT participates in these processes. Disruption in 5-HT system during sensitive periods of development results in long term consequences. Anxiety disorders are also comorbid with another disorders, such as alcohol abuse and dependence. Therefore, alterations in 5-HT system may be also related with problematic use of alcohol.

Therefore, the aim of the present experiment was to analyze the effects of 5-HT depletion on anxiety related behavior and alcohol intake. Male and Female C57BL/6 mice were treated with a 5-HT synthesis inhibitor (PCPA; 4-Chloro-DL-phenylalanine methyl ester hydrochloride; dose:200 mg/kg i.p.) during perinatal stage (P14-17) or adolescence (P42-45) in mice. 15 days post-administration, basal anxiety was measured in the elevated plus maze (EPM) for 5 min in order to analyze if PCPA's treatment affected basal anxiety behavior. After EPM, ethanol intake was measured (g/kg of ethanol intake and % preference) using a two bottle test (10% v/v vs water; 3 sessions every 48 h) before last Ethanol intake session, animals underwent EPM test to measure basal anxiety again. Our results indicate that depleting 5-HT during adolescence but not at perinatal stage reduces basal anxiety and the alcohol intake in females. Further experiments are needed in order to further analyze the effects of 5-HT depletion on risk taking behavior and neural activity.

ADOLESCENT BINGE ETHANOL EFFECTS ON CHOLINERGIC AND GABAERGIC INTERNEURONS IN THE PREFRONTAL CORTEX, STRIATUM AND AMYGDALA

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Underage binge drinking of alcohol in humans is associated with altered behavior and cognition later in adulthood. Moreover, rodent studies have linked binge-like adolescent intermittent ethanol (AIE) to adult deficits in inhibitory control, behavioral flexibility, and memory encoding, along with changes in neuroimmune signaling, synaptic plasticity and neurogenesis. AIE exposure reduces choline acetyltransferase (ChAT)-expressing neurons in the basal forebrain, and the loss of ascending projections may lead to behavioral and cognitive deficits. However, it is unknown if AIE reductions in cholinergic phenotype are exclusive for projection neurons or extend to cholinergic interneurons (ChI) and parvalbumin-expressing interneurons (PVI). These interneurons are key regulators of network function by modulation of local circuits and are important in motor and cognitive function. We hypothesized that AIE exposure decreases ChI and PVI in the PFC, striatum and amygdala relative to controls. We exposed male rats to ethanol or water during adolescence (5g/kg, 2-days-on/2-days-off, P25-55). When rats reached adulthood (~P85), brains were removed and processed for immunohistochemical visualization of ChAT+ or PV+ cells. ChAT+ interneurons were counted in PFC (orbitofrontal and medial) and striatum (dorsomedial, dorsolateral and ventral). However, we found no statistical difference in cell counts from AIE-exposed and control rats in any of these regions (simple t-tests, all p's>0.15). PV+ cell counts are ongoing, and partial results show no effect of AIE on PV+ cells in the PFC and amygdala, but a tendency toward increased PV+ cells in striatum after AIE (n=3/group). The data to date do not support our hypothesis that AIE decreases ChAT+ interneurons relative to control animals in forebrain regions. Thus, while cholinergic projection neurons are sensitive to AIE, ChI are not, highlighting the relevance of projection neurons in the cognitive and behavioral deficits observed after AIE. However, this conclusion may change if differences in PVI are found. Since ChI and PVI regulate network functioning and motor and cognitive function, AIE-induced changes in these neurons could contribute to deficits observed after AIE.

CANNABIDIOL CAUSES DECREASE IN ETHANOL SEEKING AND BRAIN SYNAPTIC CHANGES

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Drug abuse reached considerable proportions in the last years. Studies have shown that cannabidiol (CBD) has anxiolytic, anti-psychotic, antidepressant and neuroprotective properties. There is also evidence that CBD can reduce drug taking and seeking behavior. Despite of the relevance, little is known about the effects of CBD on ethanol (EtoH) use disorders. This study aimed to investigate the effects of CBD treatment upon EtoH consumption and molecular changes in the hippocampus. We used male Wistar rats that were grouped in 4 groups: a) air + vehicle; b) air + CBD 10mg/Kg; c) ethanol vapor + vehicle and, d) vapor + CBD 10mg/Kg. Animals underwent vapor chambers and received CBD 10 mg/Kg 30 minutes before each operant self-administration sessions. After the end of the treatment, animal´s brains were removed, and the Western Blotting protocol was performed to analyze PSD95 and ARC proteins expression. Our behavioral results demonstrated that CBD treatment did not decrease the number of lever presser ($F_{(3,30)}$=0.96, $p > .05$), reinforcements ($F_{(3,30)}$=0.58, $p > .05$) and ethanol consumption ($F_{(3,30)}$=1.20, $p > .05$) during the self-administration training neither blocked the ethanol escalation in the vapor exposed groups. However, our results demonstrated that CBD treatment attenuated context-induced the reinstatement of ethanol seeking ($F_{(1,41)}$=21.40, $p < .001$). Our molecular results did not demonstrate any changes in PSD95 ($F_{(3,26)}$=0.20, $p < .05$) neither in the ARC expression ($F_{(3,27)}$=1.18, $p > .05$) among the groups. This study demonstrated that CBD at the dose of 10 mg/Kg caused decreased EtoH seeking and that this treatment does not cause changes in synaptic proteins in the hippocampus.

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THE OFFSPRING OF RATS SELECTED FOR HIGH OR LOW ETHANOL INTAKE AT ADOLESCENCE EXHIBIT DIFFERENTIAL STRESS-INDUCED ETHANOL INTAKE AT ADULTHOOD

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Alcohol (ethanol) use is ubiquitous in adolescents, yet only some of them transition from regular to problematic drinking. It is important to understand why the risk for problematic drinking varies across sub-groups of adolescents. We had previously executed a short-term selection program to generate Wistar rat lines (high

and low adolescent ethanol drinking, ADHI and ADLO lines, respectively) that significantly differ in ethanol drinking at adolescence. To date, the long-term effects of this selection (i.e., when tested at adulthood) were unknown. The present study reports the results of a second cohort of rats selectively bred, in the short term, for low or high alcohol drinking at adolescence. In this study, we tested the S_0 generation and filial generations 1 (S_1), S_2, and S_3 of ADHI and ADLO offspring for basal or stress-induced ethanol intake at adulthood. The effects of the selection, conducted at adolescence, were observed at adulthood, well beyond the adolescent stage in which the selection was conducted: S_1-ADHI but not S_1-ADLO male rats exhibited stress-induced drinking. These findings indicate that genetic risk of enhanced ethanol intake at young age is still present at adulthood, long after the developmental window when the interbreeding occurred. Exposure to stress at adulthood triggers the vulnerability associated with this genetic risk, an effect associated with enhanced inborn anxiety.

ENVIRONMENTAL ENRICHMENT REVERTED THE UPREGULATION OF PDYN EXPRESSION INDUCED BY PRENATAL ETHANOL EXPOSURE.

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Previous experiments showed that moderate prenatal exposure to ethanol (PEE) induces, in rats, alterations in anxiety response and adolescent voluntary ethanol consumption. Moreover, we identified an upregulation of kappa opioid system, that was accompanied with lower DNA methylation of these genes. This study assessed if rearing the litters (both dam and offspring) under environmental enrichment may inhibit the effects of PE. Pregnant Wistar rats received daily intragastric administration of ethanol 2.0 g/kg (PE group) or vehicle (PV group) in gestational days 17 to 20. From birth and until adolescence, the litters were housed in cages bigger than the standard, equipped with several objects that were rotated to keep them novel (environmental enrichment, EE), or in standard cages (non-enriched, NE). Gene expression of kappa opioid receptor (KOR) and the precursor of its ligand, prodynorphin (PDYN) was analyzed in several areas of mesocorticolimbic circuit of infant and adolescent offspring, as well as the DNA methylation of the promotor region of these genes. Moreover, we evaluated gene expression of BDNF in the same areas. PEE enhanced, in adolescents, the mRNA levels of PDYN at Ventral Tegmental Area (VTA), an effect that was inhibited by EE. This effect was associated with a lower DNA methylation in the PE-NE group. KOR gene expression at the Nucleus Accumbens (AcbN) was lower in PE vs PV subject. In Amygdala (AMY), PE-NE infants expressed higher levels of KOR, but this effect was not related to DNA methylation changes. We observed a PEE-induced downregulation of BDNF gene expression in VTA and Prefrontal Cortex (PFC). These results are suggestive of a PEE-induced upregulation of the KOR transmitter system that, at least in certain sites, seem to be regulated by alterations in epigenetic molecular mechanisms. Environmental enrichment could be a promising therapeutic to inhibit these detrimental effects of PEE.

ETHANOL EXPOSURE POTENTIALLY REVERSES SUBTLE DOPAMINERGIC IMPAIRMENTS IN C. ELEGANS EXPOSED TO LEAD DURING DEVELOPMENT

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Previous studies in rats have demonstrated that developmentally lead (Pb) exposure induces a higher susceptibility to the stimulant and motivational effects of ethanol, both responses modulated by the dopaminergic (DAergic) system. In the present study we have employed the model organism Caenorhabditis elegans to evaluate the basal slowing response (BSR), an adaptive mechanism that depends on the DA-containing neural circuit. In this test, the increase in the rate of body bends showed in the absence of food (E. Coli OP50) is compared to the movement exhibited in a food condition, as an evidence of the integrity of the DAergic neurotransmission. Accordingly, both control and developmentally-low-level Pb-exposed worms from the following strains: N2 (wild type), MT15620 (thyroxine hydroxylase (TH) knock-out) and UA57 (TH over expressing) were evaluated in the presence or absence of food. Moreover, on the basis of the differential responses to ethanol previously described in rats and C. elegans, the animals were also tested in both conditions (food/no food) after 200mM ethanol exposure. The results demonstrated that the N2 wild type animals evidenced a good discrimination between the food and no food conditions, an effect present in both groups, independently of the ethanol exposure. However, the disruption of DA synthesis in the MT15620 strain prevented the discrimination of both conditions in the control and Pb-exposed groups, an effect reversed selectively in the latter in the presence of ethanol. Interestingly, the UA57 strain showed a reduced food/no food ratio in both groups of animals (as compared to the N2 strain), an effect that seemed to be improved after ethanol addition, particularly in the Pb-exposed group. Overall, these results highlight the importance of a normal DA functionality in the BSR test, with ethanol playing a preponderant role in this behavior, particularly in the Pb-exposed animals in conditions of altered DAergic functionality; a finding probably related to the drug-stimulating effects that we have previously reported in these animals.

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EFFECT OF ETHANOL ON THE MORPHOLOGY OF PARVALBUMIN INTERNEURONS AND THE ROLE OF NEURONAL MATRICELULAR PROTEIN HEVIN ON ETHANOL-INDUCED LOCOMOTOR SENSITIZATION IN MICE

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Addiction is a chronic relapsing disorder characterized by compulsive drug-seeking and long-term neuroplasticity in the mesolimbic system. In this regard, Hevin, which is a matricellular protein, has been implicated in synaptic plasticity associated with reward and stress resilience. Moreover, previous results demonstrated that in the striatum Hevin is only expressed in parvalbumin (PV) interneurons and astrocytes. Here, we investigate the role of neuronal Hevin in the behavioral sensitization to ethanol (Experiment 1) and the effects of chronic ethanol injection on the morphology of PV interneurons (Experiment 2). In Experiment 1, adult males C56BL6/J mice were stereotaxically injected with Hevin siRNA-expressing AAV vectors in the dorsal striatum (AAV2.2-hSyn-miRNA) and the control group was injected with GFP control virus (AAV2.2-hSyn-GFP). One month later, they were sensitized with a daily alcohol injection (1.7 g/kg, i.p.) for 13 days. Four and five days after the last ethanol injection, animals were challenge with an injection of ethanol (1.7 g/kg, i.p.) and saline (0.9%, i.p.), respectively. The locomotor activity was assessed for 20 minutes, after each challenge injection. For the Experiment 2, a virus vector with a GFP-dependent Cre recombinase (AAV2.2-Ef1α-DIO-GFP) was injected into the dorsal striatum of PVCre mice. After 30 days, PV-Cre mice were treated with a daily ethanol injection (1.7 g/kg, i.p.) for 21 days. Mice brains were perfused with paraformaldehyde 4% and confocal microscopy was used to analyze the arborization of PV dendrites in the dorsal striatum. Our data showed that inhibition of neuronal Hevin expression did not change the acute stimulatory response of ethanol (locomotion: 98.6±11.5 Sham-Saline, 246.1±59 GFPEthanol, 249.0±28.1 miRHevin-Ethanol). However, Hevin knockdown in the dorsal striatum, significantly attenuated the behavioral sensitization to ethanol when compared to controls (locomotion: 123.5 ± 28.0 Sham-Saline, 175.0 ± 29.7 ShamEthanol, 138.7 ± 15.8 GFP-Saline, 307.3 ± 40.4 GFP-Ethanol, 127.4 ± 15.4 miRHevinSaline and 200.4 ± 23.4 miRHevin-Ethanol, $p < .05$). In addition, we observed that repeated alcohol injections increased the volume of dendritic compartments of PV interneurons in the dorsal striatum (9.1±0.97 Saline, 19.1± 2.4, Ethanol, $p < .05$). Thus, our results suggest that chronic ethanol exposition alters the morphology of PV interneurons in the dorsal striatum and Hevin expression in these neurons plays a causal role in ethanol-induced behavioral sensitization.

EVALUATION OF POSSIBLE BIOMARKERS OF COGNITIVE ABILITIES, WITH EMPHASIS IN DECISION-MAKING, IN INDIVIDUALS WITH DRUG USE DISORDERS

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Drug use disorders (DUD) is defined as a set of cognitive, behavioral and physiological symptoms that configure a condition in which drug-seeking becomes a priority over other behaviors. Diagnosis is mainly dependent upon clinical symptoms, thus there is an increasing need of discovering biological markers. The present study assessed epigenetic changes on glutamatergic pathways involved in the neural networks responsible for decision-making (DM) processes, in individuals diagnosed with DUD or in controls (n = 21 and 5, respectively). The participants (diagnosed with cannabis, cocaine, or crack dependence) were submitted to test impairments in DM and morphofunctional changes in default mode network connectivity, via resting-state fMRI images. Possible changes in DNA methylation of gene promoters of glutamatergic pathways were measured in blood samples. The preliminary results suggest that the DUD group showed inferior performances than the control (mean ± SD), in the following tests: Rey Auditory Verbal Learning Test [on late evocation $F(1, 9.93) = 13.22$, $p = .005$, (6.62 ± 2.97; 10.4 ± 1.82)]; von the late [evocation after 30 minutes $F(1, 7.74) = 11.61$, $p = .001$, (6.43 ± 2.89; 10.4 ± 2.19) and on learning score (3.47± $F(1, 11.14) = 13.43$, $p = .004$, (3.57 ± 2.66; 6.8 ±1.48)]. The DUD group also spent greater time than controls in the first segment of Stroop Color Test $F(1, 23.99) = 5.23$, $p = .03$, (21.8 ± 18.0; 11.9 ± 4.02), a result suggestive of lower inhibitory control The present study suggests that individuals with DUD exhibit DM impairments, although it is still necessary to increase the number of individuals participating in each group, and to analyze morphofunctional data from neural networks and epigenetic data.

ALPHA2-CONTAINING GLYCINE RECEPTORS REGULATE ETHANOL CONSUMPTION IN MICE

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The glycine receptor (GlyR) is known to be critical for inhibitory neurotransmission in brainstem and spinal cord. Interestingly, in recent years much more attention has been focused on the presence of GlyRs in supraspinal regions. Previous studies have shown that GlyRs are potentiated by low and clinically-relevant concentrations of ethanol. Recent data from several laboratories have shown that GlyRs are important in the brain reward system and that α_1 and α_2 are the predominant subunits expressed in the nucleus accumbens (nAc). In the present study, we characterized the function of GlyRs in nAc and behavior in GlyR α_2 subunit knockout (KOα_2) mice. Because the GlyRα_2 subunit gene is located on the X chromosome, all adult males used in the study were hemizygous (-/Y) for the *Glra2* gene. KOα_2 mice exhibited normal brain weight and basal locomotor activity. However, in the accelerating rotarod assay, the latency to fall was significantly increased in KOα_2 mice compared to WT mice, indicating a difference in motor skill performance. Using electrophysiological recordings in isolated neurons, we showed that accumbal neurons in KOα_2 mice exhibited smaller glycine-evoked currents (~100 pA at 1 mM of glycine) compared to C57BL/6J mice (WT) (~500 pA at 1 mM of glycine). Also, we found a decrease in the glycinergic synaptic currents in nAc of mice lacking α_2 subunits. We also examined the effect of ethanol on sedation and drinking behaviors. When we assayed KOα_2 mice for loss of the righting reflex (LORR) in presence of 3.5 g/kg of ethanol, we found a decrease in duration (27±4 min) of LORR compared to WT mice (37±2 min). Finally, using the drinking in the dark (DID) paradigm, we showed that KOα_2 mice have higher ethanol consumption compared to WT mice. These results support the existence of the α_2 subunit GlyRs in accumbal neurons. Regarding ethanol effects, we demonstrated differences in behavioral studies, indicating the importance of the GlyRα_2 subunit as a target for alcohol in supraspinal regions. Thus, GlyRs containing the α_2 subunit are a biologically relevant target for the regulation of the reward system and the rewarding properties of ethanol.

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LEARNING EXPERIENCES COMPRISING CENTRAL ETHANOL EXPOSURE IN RAT NEONATES: EFFECTS UPON RESPIRATORY PLASTICITY AND THE BRAIN CATALASE SYSTEM

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Fetal ethanol (EtOH) exposure represents a risk factor for the Sudden Infant Death Syndrome and it's early effects upon respiration also promotes hypoxic ischemic consequences. This study analyzes central ethanol's effects upon breathing plasticity during a stage in the development of the rat equivalent to the 3rd human gestational trimester. The study not only analyzed ethanol's unconditioned breathing effects but also how they are regulated by learning processes. Taking into account that ethanol is primarily metabolized in the brain via the catalase system, we examined the effects of early history with the drug upon the activity of this enzymatic system. During postnatal days 3, 5 and 7 (PDs 3-7) pups either received intracisternal (i.c.) administrations of vehicle or ethanol (300 mg%). They were subsequently exposed to a whole body plethysmograph under normoxia. The apparatus was scented or not with the ethanol odor. The presence of the odorant increased breathing rates. The state of intoxication attenuated the onset of apneas; a phenomenon indicative of an antianxiety effect of the drug given the state of arousal caused by the novel environment, maternal deprivation and the stress of i.c. administrations. At PD9, pups were tested while sober under sequential air conditions (initial-normoxia, hypoxia and recovery-normoxia). Once again the plethysmograh was unscented or contained EtOH odor. Prior experience with the scented chamber associated with EtOH's central effects elicited a conditioned isodirectional response relative to the onset of apneas previously observed during PDs 3-7. Yet, prior history with the drug exacerbated the onset of apneas when pups were defied with hypoxia. Following this test, pups ingested 0.8 g/kg of absolute EtOH and their brains were analyzed to determine catalase activity. Pre-exposure to EtOH's central effects paired with the odor of the drug resulted in heightened enzymatic activity. The results indicate that central EtOH accumulation may exert antianxiety effects that attenuate apneic disruptions but that also has long-lasting effects upon respiratory plasticity under hypoxia. Most importantly, these effects appear to be related with how the brain catalase system reacts to the presence of EtOH in accordance with the nature of prior experiences with the drug.

EVALUATION OF AMANTADINE AS REGULATOR OF ADDICTIVE BEHAVIOUR IN A RAT MODEL OF MORPHINE ADDICTION

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Naltrexone (a non-selective opioid antagonist) is an FDA-approved drug to treat alcoholic patients, because it prevents ethanol-induced dopamine (DA) release in limbic areas resultant of the opioid-mediated removal of the tonic GABAergic inhibition exerted on these neurons. Morphine, an alkaloid derived from opium poppy, is one of the most potent analgesic substances that can also induce relaxation and euphoria but also tolerance, severe withdrawal symptoms and rewarding properties with a high risk to relapse. Like alcohol, opioids rewarding effects include pathways that involve neurotransmitters as DA, glutamate and GABA. Amantadine is a NMDA antagonist that increases DA release, with a direct effect on DA receptors and inhibition of DA reuptake, modulating glutamatergic neurotransmission which is also involved in ethanol rewarding effects. However, the effects of amantadine on the morphine-induced addiction behaviour have not been fully studied. In this study, we investigated the administration of amantadine (25mg/kg, i.p.) on morphine-induced conditioned place preference (CPP) in four groups of adult Sprague-Dawley rats. The first group received morphine (3mg/kg, i.p.) and saline (1ml/kg, i.p.), while the second received morphine and amantadine, the third amantadine and saline, and the last one was injected with saline. The conditioning phase lasted three days, injecting the assigned treatment in the morning and confining rats in one chamber for 30 minutes. After six hours, saline solution was injected, and the rats confined to the other chamber for 30 minutes. The CPP test was performed on day 4, and the results were obtained by comparing the amount of time spent in the treatment-associated chamber between the pre and post conditioning phase. In comparison to the saline group, preliminary results indicated that conditioned preference for the treatment-associated chamber was increased in the morphine and morphine-amantadine groups ($p = .04$ and $p = .008$, respectively), but not in the amantadine group ($p = .06$). There was no difference between the morphine and morphine-amantadine groups ($p = .47$). Although further experiments are necessary to confirm these results, they suggest that NMDA antagonism did not affect morphine-induced conditioned place preference, providing potential neurobiological implications in the mechanisms behind the therapeutic approaches to treat alcohol use disorders and morphine addiction.

BEHAVIORAL EFFECTS OF NOISE EXPOSURE AND VOLUNTARY INTERMITTENT ETHANOL INTAKE IN MALE AND FEMALE ADOLESCENT RATS

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Adolescence is a critical stage in Central Nervous System maturation, in which biochemical and neurotransmission changes might underlie the appearance of behavioral characteristics. Since human adolescents usually consume ethanol in the presence of noise, the use of an animal model could provide data clinically relevant. In consequence, the aim of the present work was to evaluate whether both agents were capable of producing changes in different behavioral parameters in adolescent rats. Male and female Wistar rats at early adolescence (28-days-old) were subjected to voluntary ethanol consumption for intermittent periods of 24 hours for one week, using the two-bottle choice paradigm (5% ethanol/1% sucrose). After the last ethanol intake, animals were exposed to noise (2 h, 95-97 dB) and evaluated in different behavioral tasks. Results showed that noise exposure was able to decrease associative memory (AM, ratio in EP task (T2/T1): sham: 112.2±17.8; noise: 50.7±9.1) and increase anxiety-like behaviors (Anx) in male animals (latency to open arms in EPM task (Lat): sham: 17.3±3.1 sec; noise: 26±2.1 sec). In contrast, animals subjected to ethanol intake exhibited an increase in AM (T2/T1: ethanol: 159.3±50.6) and a decrease in Anx (Lat: ethanol: 9±3 sec). When ethanol was ingested before noise exposure, no changes were observed. In contrast, females exposed to noise or ethanol showed a decrease in AM (T2/T1: sham: 131.3±19.3; ethanol: 38.5±8.2, noise: 57.5±21.6) and an increase in Anx (Lat: sham: 5.4±1.1 sec; ethanol: 37±9.1 sec, noise: 11.1±5). Similar results were achieved when female rats were subjected to ethanol intake before noise exposure. Finally, although initially animals ingested the same amount of ethanol (females: 6.5±1.1; males: 7.1±1.4, in g/kg/session), in the subsequent intake sessions females doubled the amount ingested by males (4.1±0.5 vs. 2.4±0.5, in g/kg/session). In conclusion, these results suggest that, although adolescent males and females would be equally vulnerable to the behavioral effects of noise, females would appear to be more susceptible when ethanol intake precedes noise exposure. In fact, it could be hypothesized that the compensation of the behavioral damage observed only in males would be related to the lower amount of ethanol ingested when compared with females counterparts.

SHORT-TERM SELECTION FOR HIGH AND LOW ETHANOL DRINKING DURING ADOLESCENCE YIELDS AN ANXIETY-PRONE PHENOTYPE IN THE OFFSPRING

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Alcohol use disorders are modulated by genetic factors, but the identification of specific genes -- and their concomitant biological changes -- that are associated with a higher risk for these disorders has proven difficult. Rats and mice have been selectively bred for high and low ethanol consumption during adulthood. However, selective breeding programs for ethanol intake have not focused on adolescence. This phase of development is associated with the initiation and escalation of ethanol intake and is characterized by an increase in the sensitivity to ethanol's appetitive effects and by a decrease in the sensitivity to ethanol's aversive effects, relative to adulthood. The present study performed short-term behavioral selection to select rat lines that diverge in the expression of ethanol drinking during adolescence. A progenitor nucleus of Wistar rats (S0) and filial generation 1 (S1), S2, and S3 adolescent rats were derived from parents that were selected for high (ADHI) and low (ADLO) ethanol consumption during adolescence. The S_0 generation and filial generations S_3 of ADHI and ADLO offspring were tested for sensitivity to ethanol-induced sedation and hypnosis or for shelter-seeking and risk-taking in the multivariate concentric square field test (MSCF). ADHI rats spent significantly less time in areas of the MSCF whose exploration entails risk-taking and significantly more time in dark, sheltered areas. Some of these effects were normalized by the administration of 0.5 g/kg ethanol. There were no ADHI vs. ADLO significant differences in latency to lose the righting reflex or sleep time after high-dose ethanol administration. The results suggest that the genetic risk for enhanced ethanol intake during adolescence is associated with a behavioral pattern suggestive of enhanced inborn anxiety and differential reactivity to ethanol's pharmacological effects.

HIPPOCAMPAL NEUROGENIC NICHE IN MICE PERINATALLY EXPOSED TO ETHANOL

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In humans, exposure to ethanol (EtOH) during pregnancy can cause serious alterations in morphological, behavioral and cognitive development in children which may also persist into adulthood. Children with Fetal Alcohol Syndrome (FAS) have shown distinctive, persistent and subtle patterns of cognitive dysfunction which become more pronounced with more complex psychological assessments. Previous studies in our laboratory demonstrated that rat prenatal EtOH exposure produces alterations in the morphological organization of the cerebral cortex which correlates with behavioral dysfunction. Given that adult neurogenesis has been recently postulated as a target for therapeutic approaches in neurological disorders, the aim of this work was to analyze the morphology and cytology of the neurogenic niches in the hippocampus of CD1

mice perinatally exposed to EtOH. Primiparous female CD1 mice were exposed to EtOH 6% v/v for four weeks previous to mating. Pregnant mice drank EtOH 6% v/v throughout pregnancy and during lactation. This model of maternal alcoholism rendered no significant differences between EtOH and control mice in terms of weight gain or the number of offspring. Mothers yielded a blood ethanol concentration (BEC) of 73.29±8.69 mg/dl at the end of lactation, while pups yielded a BEC of 101.56±5.21 mg/dl at P21, which shows increasing BEC in pups as compared to mothers. At P21, male pups were separated, exposed to standard food and water *ad libitum* until adulthood and never exposed to EtOH for the rest of their lives. At P0, P21 and P80, pups were perfused with formaldehyde and brains were used for immunofluorescence studies. We analyzed the morphological evolution of the hippocampus through a mathematical approach measuring circularity, roundness, thickness and cellular composition of the dentate gyrus, a hippocampal neurogenic niche. While brains exposed to EtOH showed higher circularity and roundness than controls, the thickness of the granular layer was lower than controls and persisted until adulthood when an astrocytic reaction was present, even though animals were not exposed to EtOH after weaning.

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ALCOHOL USE DURING PREGNANCY: A PREVENTION PROGRAM BASED ON COMMUNITY-HEALTH VOLUNTEERS EXPERIENCES

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Epidemiological data from several countries reveal that alcohol use during pregnancy is still highly common between women. This situation demands more effective prevention strategies, due to the great risks for the fetus development related to alcohol consumption. In Argentina this situation becomes more complex due to issues associated to accessibility to the public healthcare system. The main goal of the present work was to design a prevention strategy for alcohol use during pregnancy and breastfeeding periods, which were community-based and directed to women users of the public healthcare system, living in marginalized populations of Córdoba (Argentina). In order to acquire a deepen knowledge about the real needs of women from our communities, we performed a series of collaborative, interactive workshops with community-health volunteers. The topics of these meetings were alcohol-use related effects during pregnancy and breastfeeding periods, including biological and epidemiological information. We also discussed on popular beliefs about alcohol use during these periods that are commonly heard and routine practiced in our communities. More importantly, we discussed about women sexual and reproductive/non-reproductive health as a way of promoting healthy practices during pregnancy and breastfeeding. The accessibility to the healthcare system and the full exercise of sexual and reproductive/non reproductive rights were considered the main barriers to guarantee healthy practices during pregnancy and breastfeeding periods in women from our communities. According to the discussed content on these workshops series, and with the collaboration of the community-health volunteers, we performed a divulgation notebook which includes: information about risks related to alcohol use during pregnancy and breastfeeding periods; contact information about community-directed activities carried out

by the main public healthcare institutions; and information about sexual and reproductive/non-reproductive rights of women in accordance to our national current laws. We conclude that an effective prevention strategy for alcohol use during pregnancy and breastfeeding should be based on a more complex, integrative view about women's health, including community-based interventions and sexual education contents. Grants: SEDRONAR, convenio Fundación Abriendo Corazones Resol-2018-496-APN-SEDRONAR.

SENSITIZATION TO ETHANOL'S DISRUPTIVE EFFECTS UPON EARLY BREATHING PLASTICITY ASSOCIATED WITH HYPOXIA AND HYPERCAPNIA.

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Ethanol (EtOH) consumption during pregnancy and lactation represents a risk factor related with the Sudden Infant Death Syndrome (SIDS). This phenomenon has promoted research linking prenatal EtOH effects on the respiratory system during early ontogeny. It should also be noted that prolonged episodes of neonatal respiratory depression represent a risk factor in terms of hypoxic-ischemic effects with negative consequences on brain development. In a first study during postnatal day (PD) 9 we analyzed the impact of different doses of EtOH (0.0, 0.75, 1.37 or 2.0 g/kg) upon the respiratory response and the potential psychomotor effects in pup rats pre-exposed or not to 2.0 g/kg of EtOH during PDs 3-7. At PD 9 animals were also subjected to sequential air conditions defined as initial normoxia, hypoxia and recovery normoxia. In a second study we analyzed the blood of animals only exposed to 0.0 or 2.0g/kg of EtOH during PDs 3-9 (not subjected to a hypoxic event). The aim was to examine if mere intoxication with a moderate dose of EtOH is capable of modifying blood metabolic patterns associated with hypoxia or hypercapnia. In the first study during PDs 3-7 EtOH exerted a depressant effect upon breathing frequencies. These animals also showed a progressive sensitization effect relative to the depressant effects of the drug and lesser levels of apneas. At PD 9 dose dependent respiratory depressions were observed when pups were challenged with a hypoxic event. Independently from prior experience with EtOH, drug treatment at PD 9 significantly disrupted respiratory frequencies particularly during the hypoxic and the recovery normoxia phases. Respiratory disorders triggered by these air conditions have been implicated in the pathophysiology of SIDS. These results show that breathing plasticity is disrupted during a critical stage where respiratory alterations may lead to hypoxia-associated syndromes that endanger brain development. In terms of psychomotor activity, animals exposed to 2.0 g/kg of EtOH at PD 9 showed heightened duration and frequency of grooming. In the second study animals exposed at least one time to EtOH exhibited lower pH and higher CO_2 than animals that were never exposed to EtOH. This results suggest metabolic acidosis probably due to EtOH-related hypercapnia during a vulnerable stage in development relative to SIDS.

PLACENTAL DYSMORPHOLOGY AND ABNORMAL ANGIOGENESIS AT MID- AND LATE GESTATION FOLLOWING MATERNAL ALCOHOL CONSUMPTION IN MOUSE.

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From mid-gestation onwards, the placenta is the essential organ for supplying nutrients and oxygen to embryo-fetal development. Since placental defects correlate strongly with abnormal brain, heart and vascularization, the embryo-fetal developmental disorders after maternal alcohol ingestion may be linked to placental dysmorphology and abnormal angiogenesis at or after mid-gestation. We aimed to evaluate wether perigestational alcohol consumption up to early organogenesis (day 10 of gestation, D10), in mouse, alters placentation and disrupts vascular endotelial growth factor (VEGF) system of trophoblastic tissue at mid and later gestation. Murine CF-1 females were administered with ethanol 10% in drinking water (25% EDC) for 15 days previous and up to D10, or gestation continued with water until D13 (treated females, TF). Control females (CF) were administered with drinking water without ethanol. At D10, the implantation sites from TF had diminished trophoblastic growth, cellular and tissue defects, and poor labyrinthine vascularization detected by deficient invagination of allantoic blood vessels into the chorionic ectoderm (H-E, PAS). In the labyrinth of TF, VEGF immunoexpression was reduced while the receptor KDR expression was increased compared to controls ($p < .01$). At D13, TF-labyrinthine thickness was reduced respect to controls; and the most prevalent abnormalities in the TF-placenta were defective organization of the fetal and maternal blood vessels, observed by wide maternal blood spaces and reduced fetal capilarization. After alcohol intake cessation, D13-placental VEGF expression increased in TF-labyrinth compared to controls ($p < .05$, IHC, WB), but the receptor KDR expression did not change. These results show that perigestational alcohol intake up to organogenesis induces abnormal angiogenic pathways that may be involved in poor labyrinthine development and vascularization, at early and late gestation, and suggest that placental defects may contribute to embryo-fetal abnormalities and intrauterine growth restriction typical of FASD.

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PRENATAL ETHANOL EXPOSURE MODIFIES LOCOMOTOR ACTIVITY AND INDUCES SELECTIVE CHANGES IN MET-ENKEPHALIN CONTENT IN ADOLESCENT RATS

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Prenatal ethanol exposure (PEE) facilitates alcohol acceptance and intake, suggesting that ethanol in utero may increase the probability of drug abuse during adolescence and adulthood. Alcohol reinforcement involves the ethanol-induced activation of opioidergic systems in mesocorticolimbic areas. Changes in opioid neurotransmission may be relevant during ethanol intoxication, as well as in the adaptive neural responses induced by the drug. Some studies have assessed the possible changes in opioidergic systems as a function of ethanol exposure in adolescent animals. However, PEE effects upon locomotive responses elicited by an ethanol challenge and modulation of neurotransmission of opioidergic systems remain to be understood. This work assessed the susceptibility of adolescent rats to prenatal and/or postnatal ethanol exposure in terms of locomotive responses, as well as alcohol-related effects on Methionine-enkephalin (Met-enk) expression in brain areas related to drug reinforcement. Pregnant rats received a daily intragastric administration of ethanol (2 g/kg) or water, during gestational days 17-20. Adolescents at postnatal day 30 (PD30) were tested in a first baseline trial (habituation session) and evaluated in terms of spontaneous activity. Thereafter, animals received an ip injection of vehicle (saline 0.9% w/v) (vehicle session) and were immediately evaluated in terms of activity during 30 min. After this second trial, animals from both prenatal treatments were injected with ethanol (1.0 g/kg ip) or saline, and locomotor activity was immediately assessed for 30 min (drug session). Met-enk content was quantitated by radioimmunoassay in several brain regions: ventral tegmental area [VTA], nucleus accumbens [NAcc], prefrontal cortex [PFC], substantia nigra [SN], caudate-putamen [CP], amygdala, hypothalamus and hippocampus. PEE significantly reduced rearing responses. Ethanol challenge at PD30 decreased horizontal locomotion and showed a tendency to reduce rearings and stereotyped behaviors. PEE increased Met-enk content in the PFC, CP, hypothalamus and hippocampus, but did not alter peptide levels in the amygdala, VTA and NAcc. These findings suggest that PEE selectively modifies behavioral parameters at PD30 and induces specific changes in Met-enk content in regions of the mesocortical and nigrostriatal pathways, the hypothalamus and hippocampus. Prenatal and postnatal ethanol actions on motor activity in adolescents could involve activation of specific neural enkephalinergic pathways.

EFFECTS OF CAFFEINE AND/OR ETHANOL EXPOSURE DURING DEVELOPMENT ON ANXIETY-LIKE BEHAVIOR AND LEARNING AND MEMORY OF ADOLESCENT MICE

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In spite of epidemiological evidence of the concomitant use of caffeine and ethanol by pregnant women, the consequences of this combined exposure during development have received little attention in experimental studies. In this work we investigated the effects of co-exposure to caffeine and ethanol during development on the anxiety-like behavior, learning and memory, and cortical levels of oxidative stress of adolescent mice. Adult female Swiss mice received one of two concentrations of caffeine (0.1g/L; n=14 or 0.3g/L; n=12) in the drinking water during 7 days before mating. Exposure persisted until their pups were 21 days-old. Control mice (n=10) had ad libitum access to tap water. Every other day, from PN2 to PN8, animals in each litter were injected (i.p) with one of the following solutions: 0.25 µl/g ethanol (ETOH25), 0.5 µl/g ethanol (ETOH50) or saline solution (SAL). From PN30 to PN35 mice were submitted to behavioral tests. Anxiety-like behavior was assessed in elevated plus maze test (EPM) and learning and memory in passive avoidance paradigm (PA). On PN9, cortical levels of oxidative stress were evaluated by the measurement of thiobarbituric acid reactive species (TBARS), antioxidant capacity (DPPH) and protein carbonylation. In EPM, ethanol promoted a dose-dependent decrease in anxiety-like behavior, mice from ETOH50 group spent less time and had fewer entries in open arms than those mice from ETOH25 and SAL groups. Interestingly, in the group of mice exposed to 0.3 g/L of caffeine, anxiety-like behaviors were not affected by ethanol exposure. While caffeine did not affect behavior of mice in PA, learning and memory deficits were found only in males exposed to ethanol. In spite of ethanol did not change oxidative stress levels, caffeine had a marked antioxidant effect in all oxidative stress assays. Our data corroborate other studies that show that early exposure to ethanol promotes a number of neurobehavioral disorders. Furthermore, we suggest that caffeine exposure during development has a protective effect on deleterious effects of ethanol.

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ELSA COHORT 2014: ACUTE ALCOHOL EFFECT ON INHIBITORY CONTROL, REWARD SENSITIVITY AND RISK TAKING IN COLLEGE STUDENTS WITH HIGH AND LOW TRAIT IMPULSIVITY

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Introduction: Impulsivity and risk taking are core constructs to understand alcohol-related behaviors. Alcohol consumption is greater in those exhibiting relatively high levels of impulsivity and risk taking, and alterations in impulsivity and risk taking have been reported after acute alcohol ingestion. **Aim:** To examine the acute effect of ingested alcohol (0.6/0.7 g/kg in women and men respectively, equivalent to the expected breath alcohol concentration after a binge drinking episode) on inhibitory control, reward sensitivity and risk taking in students with high (IMP+) or low (IMP -) trait impulsivity. **Methodology:** 85 college students from the ELSA cohort 2014 (43 women, aged 21-27 years old [Mean age=22.74±1.51]) completed the BART (risk taking), GoStop (inhibitory control) and SKIP (reward sensitivity) tasks, before and after the consumption of an alcohol or a placebo drink. ELSA is a large, longitudinal study that analyzes alcohol-related behaviors in Argentinean college students. **Results:** Alcohol increased risk taking in women but not in men and induced a poorer inhibitory control, a result which was more pronounced in men than in women. Reward sensitivity was similar regardless alcohol or placebo. The hypothesis of greater behavioral impulsivity in those exhibiting higher trait impulsivity was partially corroborated. An interesting result was the differential effect of alcohol treatment on BrACs and subjective perceived intoxication between men and women. Specifically, women who received alcohol reached lower BrACs than men, but they felt more intoxicated and felt more intensely the sedative effects of alcohol than men. **Conclusions:** Alcohol induced increases in impulsivity and risk taking in a sex-dependent manner. Women were more sensitive to the acute effects of alcohol on risk-taking while men were more sensitive to the effects of the drug on inhibitory control. These results show that men and women are differently vulnerable to the toxic effects of alcohol on different indicators of behavioral impulsivity and risk taking.

ETHANOL EXPOSURE AND THE IMPAIRMENTS ON LEARNING AND MEMORY BEHAVIOR ASSOCIATED WITH DIFFERENTIAL GENE REGULATION IN ZEBRAFISH BRAIN

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Alcohol use harm process of learning and memory in humans and other animals. This drug consumption can cause brain damage after few exposures. In this context, animals models, like zebrafish (*Danio rerio*), has emerged as model organisms to study behavioral and molecular mechanisms of diseases, including those

related to the Central Nervous System. This study aimed to evaluate the effects of ethanol on learning and memory consolidation and their relationship with the regulation of target genes in the brain. We performed an Object Recognition Behavioral Test (OR) in 108 adult zebrafish (*Danio renio*). In the first step - Familiarization Phase (FP) -, animals were exposed for 10 minutes to two identical objects. After FP, the animals were divided into two groups: Control (C) and Treatment (T), exposed to water and ethanol (1%, v/v), respectively, for 20 minutes. In a second step - Test Phases (TP) – animals of both groups were exposed to the familiar object and a novel one 2 hours (TP2), 24 hours (TP24) and 8 days (TP8) after the exposure. At the end of each TP, 16 animals of each group were euthanized to brain collection and transcriptional quantification of target genes by qPCR. Regarding behavioral analysis, in TP8, the C group spent more time exploring the novel object when compared to TP2. For animals of the T group, we could not observe any difference when compared to Control or between TFs. For molecular results, in TP8 all genes showed a decrease in their mRNA transcription, comparing T to C. In TP24, we observed downregulation of *grin1a*. For both groups – C and T - we found an up-regulation of *lrfn2* in TP8 in relation to TP2 and TP24. We suggest that ethanol influence gene regulation after an acute alcohol treatment. In behavioral analysis, considering data dispersion and the lack of difference for animals in T group, suggesting that individuals in this group may have different responses to alcohol effects. A multivariate analysis will be conducted to generate scores based on different behaviors. These data will be used to divide animals of group T into new subcategories.

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UNDERNUTRITION FETAL PROGRAMMING NOT PREDISPOSE ALCOHOL CONSUMPTION IN ADOLESCENTS MALE RATS.

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Maternal undernutrition before weaning of the offspring yields detrimental effects on development, and shapes psychobiological responses later in life. The latter effect is referred to as fetal programming. It is possible that undernutrition during pregnancy and lactation increases the probability of later alcohol consumption. To assess this possibility, we exposed Wistar dams to standard chow during pregnancy (Control group, CTRL) or were fed throughout pregnancy with 50% of daily ad libitum consumption (Undernutrition group, UNDER). Furthermore, at birth the offspring was culled to 8 and 14 pups in CTRL and UNDER groups, respectively. Both groups of mothers were given ad libitum food and water until weaning day (25 days of life). The offspring was tested for alcohol consumption in 3 double bottle (24-hour) tests (5% alcohol vs. water; postnatal days 26, 28 and 30). In each session animals were weighed before and after the test, and water, alcohol and food consumed were recorded. The amount of alcohol consumed in gr/kg and the percentage of alcohol preference over water were calculated. ANOVAs showed no effect of fetal programming on alcohol consumption. A negative correlation, however, was found between food consumption and growth versus alcohol consumption (i.e., more alcohol consumption at test, less food consumption and less growth). Overall, the results show that fetal and prepubertal undernutrition did not affect alcohol consumption in adolescent male Wistar rats.

EFFECT OF IMPULSIVITY, RISK TAKING AND COGNITIVE BIAS ON ALCOHOL USE IN CHILDREN AND ADOLESCENTS

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The present study examined the association of trait and behavioral impulsivity, risk taking and cognitive bias on frequency and quantity of alcohol in children and adolescents. Participants were children and adolescents (n = 90; M age = 14.34 SE = .17; 50% female) that took part in a larger longitudinal study (N = 1762; M age = 12.59 SE = .03; 45.7% male) were they completed the UPPS-P, a 5-factor measure of trait-like impulsivity. Participants with the highest (i.e., superior quartile) and the lowest (i.e., inferior quartile) scores on the UPPS-P were invited to participate in the present study. Participants completed a paper-and-pencil survey measuring sociodemographic variables and alcohol drinking (drinking frequency and quantity) and three computerized tasks to assessed risk taking (Balloon Analogue Risk Task [BART]), response inhibition (Go Stop Task) and cognitive bias towards alcohol signals (Emotional Stroop). Participants completed the tasks in individual sessions. Results of bivariate correlations showed that age, lack of premeditation (one of the five dimensions of trait-like impulsivity), and risk taking were significantly positively associated with frequency of alcohol use; while only age was significantly associated with quantity of alcohol use. We conducted a hierarchical regression analyses I including age and trait-like impulsivity in the first step and risk-taking, response inhibition and cognitive bias included in the second step. For frequency of alcohol drinking as the dependent variable, all these variables explained 47% of the variance. Age, trait-like impulsivity and risk-taking had a significant positive effect on frequency. For drinking quantity as the dependent variable, only age and trait-like impulsivity was significantly positively associated with greater alcohol use (R 2 = .29). Altogether, these findings failed to find a robust effect of multiple measures of impulsivity on underage drinking, particularly drinking quantity. This is probably related to the low prevalence of drinking behaviors at this early age. Notably, trait-like impulsivity and risk taking had a significant effect on drinking frequency even after controlling or chronological ager; suggesting these variables are relevant to discriminate and identify children and adolescents at greater risk for engaging in alcohol use.

REDUCED AVAILABILITY OF THE ALDH COFACTOR NAD+ BY ROTENONE IN A *CAENORHABDITIS ELEGANS* MODEL: FUNCTIONAL RELEVANCE FOR THE METABOLISM OF TOXIC ALDEHYDES

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The ALDH superfamily is associated with physiological and pathological processes. These enzymes play a key role in toxic aldehydes disposition, not only of those generated by oxidative stress (such

as 4-hydroxynonenal) and central and systemic ethanol metabolism (acetaldehyde), but also products of biogenic amines degradation, including DOPAL (3,4-dihidroxyphenylacetaldehyde), dopamine (DA) first metabolite. The mitochondrial ALDH2 isoform is the best described due to its role in ethanol metabolism. Less known is a new body of research suggesting that ALDH2 dysfunction may contribute to a variety of human conditions including aging, neurodegenerative diseases and cancer. In this line, benomyl (a fungicide that directly inhibits ALDH2) and rotenone (a botanical insecticide that prevents NAD+ re oxidation in the mitochondrial complex I) have been associated with the environmental etiology of Parkinson disease. On the basis of these antecedents, in the present study we sought to describe the potential neurotoxicity of the exposure to the indirect ALDH inhibitor rotenone on the model organism *Caenorhabditis elegans*. Thus, wild type N2 worms were maintained in agar plates in the presence of food (OP50 *E. coli*) and synchronized to obtain adult animals. They were subsequently exposed to rotenone at 0, 2, 4, 6, 8 and 10 μM concentrations to perform a doseresponse curve to evaluate potential lethality of this insecticide. They were also evaluated in their size to determine potential detrimental effects in normal growing conditions. The results demonstrated that the doses selected did not evidence any effect in the worm's survival, although a reduction in size was observed with the higher doses evaluated. Current experiments are focused on the study of the basal slowing response, a behavior dependent on the DA system integrity, to later determine DA functionality in available DA and ALDH transgenic strains. Overall, we propose the present approach as a useful tool to modulate ALDH functionality, which may have important implications, not only in the field of neurodegenerative diseases but also in the deep understanding of ethanol metabolism as a potential target of the drug addictive effects.

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OMEGA-3 BUT NOT OMEGA 6 MITIGATES BEHAVIORAL IMPAIRMENTS INDUCED BY BINGE ETHANOL EXPOSURE IN RAT NEONATES

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Maternal alcohol consumption during pregnancy may cause neurocognitive and behavioral disorders that can persist until adulthood. Epidemiological data has revealed an alarming increase in the frequency of alcohol intake in pregnant women. Nutritional variables may also have an impact on the behavioral alterations occasioned by alcohol during development. Moreover, omega-3, a polyunsaturated fatty acid necessary for normal brain development, is deficient in ethanol-treated animals. Although studies have shown that omega-3 supplementation after prenatal ethanol (EtOH) treatment improves some disorders, there are no reports about acute treatment with omega-3 in binge alcohol neurotoxic models during postnatal development. The goal of this study was to determine whether an administration of omega-3, after an acute ethanol dose in neonates, would be able to attenuate alcohol effects in offspring. Male/ female rats were administered ethanol (2.5 g/kg s.c. at 0 and 2 h) or saline on postnatal day (PND) 7, with a single dose of omega-3 (720 mg/kg), or omega-6, 15 min after the last alcohol injection. It has been found that EtOH-treated animals showed hyperlocomotion and anxiety-like behavior on PND 14. Administration of omega-3 after EtOH treatment reduced hyperlocomotion and the anxiety-like behaviors on PND 14. On the other hand, animals treated with omega-6 did not reduce those EtOH effects. In conclusion, acute ethanol exposure induced neurobehavioral

alterations that persisted in the offspring and omega 3 mitigates those effects but not omega 6. These data are relevant considering that omega-3 treatment may have therapeutic effects through mitigating some of ethanol´s damaging consequences.

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PROTECTIVE BEHAVIORAL STRATEGIES AND ALCOHOL USE IN ARGENTINEAN COLLEGE STUDENTS: DIFFERENCES BETWEEN THE ACADEMIC SEASON AND THE SUMMER BREAK.

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Introduction: Protective behavioral strategies (PBS) reduce or minimize the negative consequences of alcohol drinking. PBS hold promise as intervention targets to reduce alcohol use and its negative consequences and, therefore, there has been an increasing interest in assessing determinants of this variable. It has been reported that women use more PBS than men and that certain contexts/seasons (e.g., Spring break vs. the regular academic season) are associated with greater use of PBS. The great majority research assessing these effects, however, comes from U.S., and very little is known about PBS determinants in South America. **Aim:** This work examined seasonal variations in the use of protective behavioral strategies (PBS) and alcohol outcomes in two distinct times of the academic calendar: 1-the spring academic semester and 2-summer break. We examined -both within each time and prospectively- the relationship between the use of PBS and alcohol outcomes. **Method:** A sample of 223 college students reported -via two online surveys -- use of PBS, alcohol use and alcohol-related negative consequences. **Results.** The use of PBS (notably, the dimension "manner of drinking") was negatively associated with alcohol outcomes, particularly in women and during spring. The frequency of use (in women only) and the weekly volume of alcohol ingested were greater during the summer. Women, but not men, reported greater use of PBS and fewer negative consequences during the summer break than at the academic season. **Conclusions.** The use of certain PBS may be associated, particularly in women, with lower alcohol consumption and alcohol-related negative consequences.

ELSA COHORT 2014: HEAVY EPISODIC DRINKING TRAJECTORIES AMONG ARGENTINEAN COLLEGE STUDENTS

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Introduction: Heavy episodic drinking (i.e., the ingestion 4/5 standard alcohol drinks in one drinking session for women and men, respectively) is prevalent in college students. In Argentina, there is a need to progress from cross-sectional to longitudinal studies to better understand changes in alcohol use during the college

years. Trajectory studies generate a progression of behavior and, by accumulating data over time, allow to identify groups that exhibit different patterns of alcohol use across time. **Aim:** to identify heavy episodic drinking trajectories in Argentinean college students during the first three years of college. **Methodology:** *Sample:* participants were 1749 college students (62.6% women) between 18 and 25 years old (M = 19.1 ± 1.7) who completed at least two of the 7 data collections carried out over three years. *Measures:* participants reported frequency of engaging in heavy episodic drinking (from less than monthly to three times a week or more) and the prevalence of several alcohol use indicators: usual quantity, usual frequency and alcohol-related negative consequences. *Data analysis*: Latent Class Growth Analysis (LCGA) was used to identify the pattern and number of heavy episodic drinking trajectories that best fit the data. **Results:** we identified five trajectories of heavy episodic drinking frequency: *Heavy Stable Frequency, Moderate Frequency, Low Frequency, Infrequent* and *Descendent Frequency*. Two of these five trajectories were relatively stable and three trajectories showed a decreasing slope over time. These trajectories were significant different in several alcohol use indicators. **Conclusions:** These trajectories partially coincide with those identified in studies from other cultures. In coincidence with previous studies, we identified the high and stable frequency trajectory, the low/near zero frequency trajectory, two moderate frequency trajectories and a descending frequency trajectory. Unlike previous studies, we did not find a trajectory with increasing/ascending heavy episodic drinking frequency. The latter may be related to contextual/cultural variables like differences in the age when the peak in alcohol consumption is reached, the legal minimum age to buy alcoholic beverages, and the idiosyncratic elements that characterize college life in Argentina.

INTAKE OF ALCOHOLIC BEVERAGES, EXPECTATIONS TOWARDS ALCOHOL, AND CONSUMPTION CONTEXTS AMONG SCHOOLED ADOLESCENTS FROM CÓRDOBA AND SANTIAGO DEL ESTERO

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The aim of this study is to analyze the amount of alcoholic beverages consumed weekly by adolescents of both sexes, schooled, residing in Cordoba and Santiago del Estero, according to expectations towards alcohol (EA) and consumption contexts (CC), in order to determine differences and associations. The sample was of n = 259 subjects (58.30% female, 41.70% male) aged 13 to 18 years (mean = 16.24, ±sd 1.32), of which 65.64% were living in Córdoba and 34.36% in Santiago del Estero. The data collection was carried out via online. The following instruments were administered: a socio-demograpihc data questionnaire (created *ad hoc*); the Alcohol Expectancy Questionnaire for Adolescents (CEA-A); and the Drinking Contexts Questionnaire – Adolescent form (CCCA-A). Rstudio was used for data analyses. Non-parametric statistics were applied to analyze differences (Wilcoxon test: W) and associations (Spearman correlation coefficient: rho). Type I error was set at ≤ 0.05. No significant differences (p-value < 0.05) were found between the scores obtained by the Cordoba and Santiago del Estero participants in positives EA (which include the factors: sociability, relaxation, and sexuality), in negatives EA (which include the factors: deterioration, risk and aggressiveness, and negative states), and in almost all the CC factors (social facilitation, peer group acceptance, and parental

control), except for stress control, in which the Córdoba participants scored significantly higher than those of Santiago del Estero (W = 8943.5, p-value = 0.01216). The average amount of alcoholic beverages (measured in glasses) consumed by adolescents per week was 5.17 glasses (±sd 4.48; median = 4), and did not differ significantly by province (W = 6274, p-value = 0.5964). In all the sample, higher intake of alcoholic beverages was associated with higher positive EA score but also with higher negative EA score, and with all the CC factors (p-value < 0.05). Part of these findings are contradictory to the literature reporting that negatives EA, unlike positives EA, would be associated with lower alcohol consumption in adolescents.

IMPULSIVITY AND ALCOHOL EXPECTANCIES: ASSESSMENT OF THE ACQUIRED PREPAREDNESS MODEL FOR ALCOHOL USE IN TEENAGERS

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Introduction: Alcohol is the psychoactive substance with the highest levels of consumption among Argentinian teenagers. It is a concern, because 13% and 25% of teenagers show heavy episodic drinking ([HED]; i.e., 4/5 standard alcohol drinks in one drinking session for women and men, respectively). Two variables related to alcohol consumption are impulsivity (a multidimensional concept that includes several behaviors, such as being unable to inhibit a response, act without planning, difficulty on estimating consequences on a particular behavior, among others) and alcohol expectancies (beliefs about positive and negative effects of alcohol use on behavior, mood and emotions). The Acquired Preparedness Model (APM) integrates both variables by stating that people with higher levels of disinhibition are prone to learn the positive reinforcements of alcohol consumption, leading to higher levels of alcohol use. There are no studies that have examined the APM in Argentinian adolescents using a multidimensional model of impulsivity. **Aim**: To examine the mediational role of alcohol expectancies in the association between impulsivity (using a multidimensional model of impulsivity, the UPPS-P) and frequency of HED in teenagers from Buenos Aires (Argentina). **Methodology:** A sample of 427 high-school students (58% women, aged 13-18 years old [M = 15.72 + 1.48]) from Buenos Aires (Argentina) took part of the study. Participants reported frequency of engaging in HED and measures to assess trait-like impulsivity (UPPSP) and alcohol expectancies. **Results:** HED is highly prevalent (i.e., close to half of teenagers) among this sample. Data showed adequate fit to the APM model (CFI = .980; p = .0318; RMSEA = .067 [IC 90 0.018, 0.121]). Specifically, results confirmed the mediational role of alcohol expectancies in the relationship between impulsivity and HED.

ANALYSIS OF NEURONAL ACTIVATION AND NEUROPLASTICITIES RELATED TO ACUTE AND CHRONIC ADMINISTRATION OF ETHANOL IN MICE

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The abusive consumption of ethanol promotes neuroplasticities and alterations in the balance between excitatory and inhibitory neurotransmitters, causing changes in proteins and resulting in modifications in the neuronal activity. In the present study, we used male Swiss mice and performed behavioral analysis of the development and expression of locomotor sensitization induced by ethanol. After behavioral analysis, we evaluated neuronal activation in the medial prefrontal cortex (mPFC) (cingulate, prelimbic and infralimbic), nucleus accumbens (Nac) (shell and core) and amygdale (AM) (basolateral and central) using Immunohistochemistry and also performed the quantitative analysis of the proteins: Arc, FMRP, GluR1 and PSD-95 by Western Blotting. Our results demonstrated that chronic administration of ethanol induced behavioral locomotor sensitization. The acute ethanol treatment caused an increase in neuronal activation into the mPFC cingulate area. Further, chronic treatment promoted activation of the mPFC pre-limbic area and in the NAc (core and shell) and AM (basolateral and central). In the evaluation of the protein expression, our results demonstrated that acute and chronic administration caused different patterns in protein expression: in the mPFC was observed a higher expression of GluR1 and PSD- 95 after chronic treatment and, in the NAc was observed a higher protein expression of Arc, GluR1 and PSD-95 in the acute treatment, and higher expression of FMRP after the chronic treatment. We conclude that different neuronal projections are activated and depend on the duration of the treatment. In addition, we demonstrated the influence of ethanol on the expression of important proteins for neuroplasticity and synaptic remodeling - an extremely important mechanism for a better understanding of the mechanisms that may be involved in the transition of occasional to compulsive use of drugs of abuse.

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THE IMPACT OF MILD ALCOHOL CONSUMPTION ON SOCIAL COGNITION IN ECSTASY USERS

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Social cognition has been a neglected area of research within the field of substance use. This study assessed the relative contribution of alcohol, cannabis, psychedelics and ecstasy use on several dimensions of empathy. Our sample consisted of 21 ecstasy users whose only drug of use other than ecstasy was cannabis, psychedelics or alcohol. Empathy was measured via the short version of the Empathy for Pain Task (EPT),

which assesses 4 dimensions of empathy (i.e. empathic concern, degree of discomfort, behavior of the perpetrator and punishment) in 3 (neutral, intentional and accidental) conditions. We employed drug use questionnaires and the ASSIST scale to assess the level of drug abuse for each substance. We constructed a multiple regression model for each of the dimensions of the EPT considering both the response and reaction time of the subjects. We selected only one predictor variable from each substance and employed a stepwise selection method. Subjects showed a mild alcohol consumption pattern as indicated by standard units of alcohol consumed in the last month (M = 4.06, SD = 3.26). Alcohol-related variables were the only variables that significantly predicted the responses in "the degree of discomfort" (R^2 = .59, t = -3.70, p < .01)and "behavior of the perpetrator" (R^2= .46, t = -2.98, p < .05) dimensions of the intentional condition, and in the "degree of discomfort" (R^2= .41, t = -2.71, p < .05) and "punishment dimensions" (R^2= .47, t = 2.99, p < .05) of the accidental condition. A negative association was found for these variables (i.e., more alcohol use, less empathy scores) except from the punishment dimension. Moreover, the alcohol subscale of the ASSIST was negatively associated with empathic concern (R^2= .29, t = 2.18, p < .05), in the intentional condition. Alcohol-related variables accounted for only a minimal proportion of the variance in the empathic concern dimension, of both the intentional (β= -.011, t = -.37, p < .05) and accidental condition (β= -.024, t = -.69, p < .05). Overall, these results suggest that, in ecstasy users, even low levels of alcohol use – but not of cannabis or psychedelics -- may have a significant impact in social cognition abilities.

INTERACTIVE EFFECT OF NICOTINE AND ALCOHOL ON ALCOHOL-SEEKING BEHAVIOR IN A RAT MODEL OF ALCOHOL CONSUMPTION

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Alcohol and nicotine are the most commonly co-used psychostimulants. Clinical observation and animal research indicate a bidirectional actions between alcohol and nicotine consumption. In light of a close temporal relationship of tobacco smoking with alcohol use, it is hypothesized that nicotine may function as an occasion setter for alcohol-seeking behavior. The present study examined the effect of nicotine on the perseverance and relapse of alcohol-seeking behavior in a rat model of alcohol consumption. Male Sprague-Dawley rats were trained in daily 30-min sessions to press a lever for oral self-administration of alcohol at 10% concentration in water. A sensory stimulus was associated with each alcohol delivery and thus became a discretely conditioned cue. Five minutes prior to the sessions, rats received a subcutaneous administration of nicotine at 0.2 mg/kg. In the subsequent extinction test sessions, alcohol was unavailable with or without nicotine or the cue. The reinstatement tests were performed on the following day after the extinction criterion was met. Continued administration of nicotine sustained responses on the previously alcohol-reinforced lever in the extinction tests. Re-administration of nicotine after extinction reinstated lever responses. In both the extinction and reinstatement tests, a combination of pre-session nicotine administration and in-session alcohol cue presentation produced a more robust behavioral effect than either nicotine or cue alone. These data demonstrated an interactive effect of nicotine with alcohol on alcohol-seeking behavior. The findings suggest that tobacco use may contribute to the perseverance of and relapse to alcohol-seeking behavior in abstinent alcoholics.

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THE ASSOCIATION BETWEEN FREQUENCY OF MARIJUANA USE AND MARIJUANA-RELATED NEGATIVE CONSEQUENCES IN ARGENTINEAN COLLEGE STUDENTS.

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Marijuana use, which is highly prevalent among college students, is associated with low academic performance and with greater risk of developing poor mental health (including depression). All these negative consequences seem to be positively related to higher frequency or intensity of marijuana use. The present study aimed to describe the frequency of marijuana use in Argentinean college students and examined its association with marijuana-related negative consequences. Argentinean college students who reported at least one episode of marijuana use during the previous year (n = 130, 72.3% women; M age = 23.02 ± 3.04 years) completed an online survey that measured marijuana frequency use in the past 12 months (from 1 = *once-twice a year* to 12 = *four or more times a week*) and marijuana-related negative consequences. Marijuana-related negative consequences were assessed via the Marijuana Consequences Questionnaire (MACQ). The MACQ is a 50-items scale grouped in eight subscales: Social-interpersonal Consequences, Impaired Control, Self-Perception, Self-Care, Risk Behaviors, Academic/Occupational Consequences, Physical Dependence, and Blackouts. Each item is scored dichotomously to reflect presence/absence of the NC. The total score reflects the total number of NC. Descriptive statistic was used to describe frequency of marijuana use for the total sample and as a function of sex. Bivariate correlations were conducted between the scores of MACQ's subscales and frequency of marijuana use. Results: Forty per cent of the sample reported to use marijuana between one and nine times per year (low-frequency users), 18.5% reported to use between ten times/year and twice a month (medium-frequency) and 41.5% reported to use three or more times per month (high-frequency). Frequency of use was significantly associated with negative consequences in 6 of the MACQ's scales. Specifically, positive significant associations were found between frequency of marijuana use and Impaired Control (r = .59; $p \leq .001$), Self-Perception (r = .21; $p \leq .05$), Self-Care (r = .48; $p \leq .001$), Academic/Occupational Consequences (r = .37; $p \leq .001$), Physical Dependence (r = .49; $p \leq .001$), and Blackouts (r = .19; $p \leq .05$). Discussion: The present findings showed that frequent use of marijuana significantly increased the risk of experiencing a broad myriad of negative consequences. Notably, 41.5% reported to consume marijuana at a frequent basis, suggesting these students might be at risk for developing marijuana-related problems. Frequent marijuana users should be identified and targeted for intervention.

ELSA 2016 COHORT: ALCOHOL, TOBACCO, AND MARIJUANA USE IN ARGENTINEAN COLLEGE FRESHMEN

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Emerging adulthood is the developmental stage between adolescence and young adulthood that involves exploration of life alternatives concerning love, work and interests as well as instability. This stage, and particularly, the transition from high school to university life, is considered a high-risk stage for the initiation and escalation of substance use. Culture and particular idiosyncratic features of college life may potentiate or interact with these transitions leading to different substance use outcomes. There are, however, noticeable differences in college life between Argentina and US, the country that concentrates the vast majority of research on substance use during the college years. The present cross-sectional study describes the occurrence of alcohol, tobacco, and marijuana use in a large sample of Argentinean college freshmen (n = 4083, 40.1% men; M age = 19.39 ± 2.18 years). Participants completed a survey that measured substance use (alcohol [with a focus on heavy drinking and binge drinking behaviors], tobacco, and marijuana). Results: The findings indicated that alcohol use is nearly normative (90.4 and 80.3% with last year and last month use, respectively) and heavy episodic drinking is highly prevalent (68.6).Tobacco use (51.3 and 36.3% lifetime and last year use, respectively) and marijuana use (36.0 and 27.5% lifetime and last year use, respectively) was lower than alcohol use. The analysis of sex differences in the frequency of heavy episodic drinking and frequency of tobacco and marijuana use showed that men and women exhibited a fairly similar prevalence of these behaviors when focusing on less-than weekly use. Discussion: A main contribution of this study was the description of substance use behaviors in a large sample of Argentinean college freshman (from many and different careers). Overall, results suggest that alcohol use is more prevalent in Argentina than in U.S. while the opposite applies for marijuana use.

MARIJUANA USE AND PROTECTIVE BEHAVIORAL STRATEGIES IN ARGENTINEAN COLLEGE STUDENTS

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The Protective Behavioral Strategies Scale for Marihuana [PBSM] measures the frequency of engaging in specific behaviors to reduce or minimize the negative consequences of marijuana. Previous studies, conducted mostly with college students from U.S., showed a robust association between PBSM scores and marijuana outcomes. This study examined the use of protective behavioral strategies and its association with marijuana use (i.e., frequency and quantity) and marijuana-related negative consequences in 158 freshman college students (51.3% women, M age = 20.08 ± 4.18) from Argentina. College freshman that reported using marijuana at least once with the previous month completed an online survey that assessed frequency (i.e., number of

days) and quantity of marijuana use (i.e., grams of marijuana within each day of a typical week), marijuana-related negative consequences, and the PBSM. Close to 30% of the sample reported >5 days of marijuana use during the previous month and close to 20% reported using more than 3 grams during a typical week of marijuana use. Overall, marijuana use and PBS use were statistically similar between men and women. PBS was, in both men and women, negatively and significantly associated with frequency of use and – in men only – with quantity of marijuana use, but not with the number of marijuana-related negative consequences. Conclusions: Frequency of marijuana-related PBS was, unlike previous studies that assessed this variable in the context of alcohol use, similar between men and women. Moreover, and despite a general protective effect of PBS on marijuana use, the association between PBS and marijuana use seems to be stronger for men than for women. The promotion of PBS seems a promising intervention to reduce marijuana use

ANALYSIS OF CHANGES IN COGNITIVE CAPACITIES, FOCUSING ON DECISION-MAKING, IN INDIVIDUALS WITH ALCOHOL USE DISORDER

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Ranked as the seventh-highest risk factor for death are alcohol use disorders. Genetic and environmental factors influence the disorder's multifactorial character. The neural structures than undergo the most neuro-plasticity by alcohol effects are those involved with the reward, stress and cognition. Cognition, precisely the decision-making (DM), targets the deleterious alcohol effects leading to substance-seeking behaviors. This project has been developed with the objective to analyze possible changes in cognition, focusing in DM, through cognitive and emotional tests analysis in individuals with AUD. Individuals diagnosed with AUD and control (CO) have responded to cognitive tests (Iowa Gambling Task-IGT, Rey Auditory Verbal Learning Test-RAVLT, and Stroop Test) and emotional tests (Beck Depression Inventory-BDI and State-Trait Anxiety Inventory-STAI). Twenty patients were collected (16 AUD, 4 CO), in which we observed a higher alcohol use score in the AUD group (27.7 ± 8.6) over the CO group (3.5 ± 7.0). Besides, the AUD had worse results compared to the CO group for the Stroop T1 test [20.6 ± 15.7; 12.2 ± 4.5], Stroop T2 [30.9 ± 33.8; 16.5 ± 5.1] and Stroop T3 [51.4 ± 62.7; 24.2 ± 8.8], as well as for the STAI-trait [48.7 ± 11.7; 41 ± 12.4] and STAI-status [40.1 ± 8.9; 39.2 ± 5.7], respectively. Moreover, we observed in the AUD group results lower than CO, respectively, for the immediate score [48 ± 10.2; 36.4 ± 10.3]; forgetfulness score [2 ± 2.7; 2.3 ± 1.7], learning score [3.5 ± 3.1; 6.3 ± 0.9] and IGT [4.4 ± 13.6; 11.5 ± 36.7]. For BDI, AUD obtained better values [12 ± 8.4] than CO [11.5 ± 8]. Until now, our results indicate that the AUD group showed worse results on tests that evaluate executive, cognitive and DM functions than the CO group. Thus, we can conclude so far that individuals with AUD present DM impairment due to the alcohol action on the neural structures that would regulate this complex process. However, is needed an increase in sample number, for data clearer and more conclusive.

REGULATION OF NEUROINFLAMMATION BY LITHIUM IN DRINKING IN THE DARK ADOLESCENT MICE MODEL

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Alcohol abuse is one of the primary risk factors for more than 200 medical conditions, including some of neuropsyquriatic disorders, and a high percentage of which (24.6%) are disabilities. The adolescence holds a critical stage of neuronal development in which the brain is highly sensible to toxic compounds. The hippocampus, brain region involve in learning and memory, is particularly sensible to the toxic effects of alcohol. Previous studies have found that alcohol induces neuroinflammation in the hippocampus and we believe that lithium, a general inhibitor GSK3B, could modulate this effect. The present study assessed the effects of lithium intake in the prevention of binge alcohol drinking induced cognitive impairment and neuroinflammation in C57BL/6 adolescent mice, by using a Drinking in the Dark (DID) consumption method. Prior and during the DID the drinking water consisted of water (SESE and SEET), or water with 5.3 meq/L of Lithium (LiSE and LiET). Starting at PND 28 until PND 45 both groups of mice consume 20% v/v ethanol solution (SEET and LiET), or water (SESE and LiSE), in cycles of 4 days of consumption (2-4h) achieving blood ethanol concentration of >100 mg/dl, and 3 days of withdrawal. Cognitive function was evaluated by Social recognition task, in both controls (SESE and LiSE), exhibited the expected behaviours for the difference in percentage of time spent with the old mice (+21.54% for SESE, and +19.78% for LiSE), and while the alcohol treatment (SEET) showed cognitive impairment (-1.61%), the alcohol with lithium treatment (LiET) showed a behaviour similar to the controls (+28.16%). This concludes that lithium is implicated in the prevention of alcohol induced cognitive impairment by recovering the preference for social novelty as well as social recognition performance.

INTERACTION BETWEEN HIGH-FAT DIET AND ETHANOL INTAKE LEADS TO CHANGES ON THE FECAL MICROBIOME

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A growing body of evidence suggests that consumption of high-fat diet or ethanol intake affecting directly the abundance and composition of the gut microbiome. In response to these changes, the gut microbiome could modulate cellular responses in the host organism that might be related to the onset of a broad range of phenotypes, such as obesity, metabolic syndrome and drug addiction. In order to evaluate the effects of high-fat diet, ethanol intake and its interaction in gut microbiome, the present study used an animal model of chronically fed with high-fat diet and free-choice ethanol intake. In the first experimental stage (T1) forty-four C57BL/6 mice were submitted dietary treatment for 8 weeks, in which 30 animals received a high-fat diet, the HSB diet and 14 animals received the AIN93G standard diet. In the second stage (T2) the animals

for four weeks were divided in six subgroups: [1] AIN93G+H2O (n = 7), [2] AIN93G+EtOH (n = 7), [3] HSB+H2O (n = 7), [4] HSB+EtOH (n = 7), [5] HSB-AIN93G+H2O (n = 8), and [6] HSB-AIN93G+EtOH (n = 8). Three groups (+H2O) had only access to water, while the remaining three (+EtOH) had a free choice between water and a 10% ethanol solution. In the HSB-AIN93G groups, the HSB diet was replaced by the AIN93G diet. Throughout the experiment the body weight, diet, ethanol consumption and adiposity index were evaluated. At the end of T2, animal feces were collected for total bacteria DNA extraction, followed by sequencing through the Illumina's MiSeq platform, and posterior analysis with the aid of bioinformatics tools. The result obtained with this model, point out that the interaction between HSB diet and ethanol intake directly affected the structure, composition and abundance of bacterial groups on fecal microbiome. In addition, the HSB consumption induced weight gain; increase in the adiposity index and *Firmicutes*/*Bacteroidetes* ratio. Finally, we also pointed out that the withdrawal of the HSB diet affects the ethanol preference. These findings suggest that interactions between high-fat diet, its withdrawal, and ethanol intake, trigger changes in the gut microbiome that might take an important role in the maintenance of the observed phenotypes as well as in the increase consumption ethanol.

SOCIAL ISOLATION INCREASES ETHANOL CONSUMPTION IN ADOLESCENT MICE

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During adolescence, social experience is crucial to the ability to exhibit appropriate social behavior in the future. Social isolation can influence brain and behavioral development in adolescence. Since ethanol consumption usually begins during adolescence, the use of this substance during adolescence may promote lasting changes in the central nervous system. Thus, the present study aimed to standardize the protocol for intermittent ethanol consumption (IA2BC) in adolescence by assessing consumption of ethanol at 10% and 20%, and whether social isolation increases adolescent ethanol consumption when compared to consumption of animals with social interaction. In this experiment, 31 male Swiss mice were divided into two experimental groups: isolated (n = 15) and grouped (n = 16). All animals underwent the IA2BC protocol, with access to ethanol 10% and 20% for 4 weeks, followed by the ethanol vapor chamber for two weeks. It was observed that in the concentration of 10%, there was an increase in the ethanol consumption by the isolated group (average: 7.8 ± 1.7 g/kg) compared to animals with social interaction (average: 6.4 ± 1 g/kg). Regarding the concentration of 20%, it was observed an increase in the consumption by isolated animals (average: 17.5 ± 3.7 g/kg) when compared to animals with social interaction (average: 4.7 ± 3.4 g/kg). These findings are consistent with the hypothesis that prolonged activation of the stress response system resulting from isolation during adolescence could lead to long-term neurobiological and behavioral disorders, which may influence substance abuse in adulthood.

PATERNAL ALCOHOL CONSUMPTION ALTERS OFFSPRING´S BEHAVIOR AND EARLY MOTOR ABILITY DEVELOPMENT

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In a previous study, we observed that male alcohol consumption affected sperm biochemical parameters. There was a delay during early embryo development in vitro of the offspring of these mice. Also, they were underweighted during the first weeks of life, recovering weight in adulthood. We detected that the mice offspring health status was somehow altered with a modification of the spleen cell population. In the present study we assessed the effects of paternal alcohol consumption on the puppy's motor ability and behavior at adulthood. For this, CF-1 male mice were exposed or not to 15% (v/v) ethanol in drinking water ad libitum for 15 days. Males, treated or not, were mated with non-treated CF-1 female mice in a ratio 1:1. Pregnancy outcome from males exposed (alcohol group, A) or not (control group, C) to ethanol was evaluated and litter mortality and organ weight registered. Developmental (Surface righting test) and behavioral tests (Open field or OF, Elevated plus maze or EPM, Object context recognition test or OCT and Social dominance tube test) were assessed. Litter from alcohol group presented a delay in surface righting, taking longer time to do it seven days after birth, compared to control group (C = 1,49 s ± 0,9817 s and A = 7,628 s ± 11,91 s, $p < .0001$). The OF test showed that males from alcohol group spent a longer time in the center of the maze than the control group (C = 28,24 s ± 7,581 s and A = 62,63 s ± 12,1 s, $p < .05$) but there were no differences within females. Control group was more socially dominant than alcohol group, both in male (C = 72 % and A = 28 %, $p < .0001$) and female (C = 63 % and A = 37%, $p < .05$) offspring. We found no differences between groups when we evaluated the offspring for OCT and EPM tests. Altogether, these results suggest that paternal moderate alcohol consumption modifies the offspring motor development, delaying the surface righting. It also modifies their behavior, impairing their social dominance and exacerbating their open field activity.

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ATTENTIONAL, EXECUTIVE, EMOTIONAL AND SOCIAL DIFFERENCES IN ADOLESCENTS AND YOUNG ADULTS WITH NON-PATHOLOGICAL SUBSTANCE USE

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Executive functions and attention are some of the capacities that are compromised in chronic alcohol dependence and substance abuse in adults (Uekermann & Daum, 2008; Crews & Boettiger, 2009). Changes in the brains of adolescent consumers can increase vulnerability to the neural effects of such substances (Clark, Thatcher & Tapert, 2008), hampering key cognitive development processes (Chanraud et al., 2007). The effects of sporadic consumption on executive functioning are not widely valued and reported. The objective of this work is search for differences in measures of executive functioning among those examined with different levels of non-pathological substance use. The consumption of alcohol and marijuana will be especially examined because are substances of greater prevalence. We evaluated 45 adolescents and young adults with university studies, without antecedents of problematic consumption or psychiatric history, with the Dysexecutive Questionnaire (DEX) and the Prefrontal Symptom Inventory (IPS) to assess disexecutive symptomatology; and The Marijuana Screening Inventory (MSI-X) and the Alcohol Use Disorders Identification Test (AUDIT) to relieve substance use The partial and total IPS's scores correlated positively and significantly with the partial and total DEX's scores, demonstrating convergent validity. The 78% of those examined were classified in the low-risk group by CITDCA and MSI-X. Positive correlations were presented between the CITDCA scores and the MSI-X. The MSI-X scores correlate with the IPS social behavior problem index. Those examined with higher score in the MSI-X show higher levels of emotional problems ($t = 2.391$; $p = .022$) and higher total IPS score ($t = 2.247$; $p = .030$), as well as a higher level of disorganization/apathy ($t = 2.038$; $p = .006$) and higher total score on the DEX ($t = 2.213$; $p = .033$). Those examined with higher score in the CITDCA have higher levels of social problems ($t = 2.452$; $p = .020$) and emotional problems ($t = 2.219$; $p = .033$) in the IPS. Even the non-problematic consumption of alcohol and marijuana could lead to attentional, executive, emotional and social differences in young and young adults of university population, with greater difficulties on those with more substance use.

THE EFFECT OF MONO- OR BIPARENTAL CARE ON ALCOHOL-INDUCED MOTOR STIMULATION AND NEURAL ACTIVATION IN INFANT MICE.

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Social experiences play an important role in offspring development. We have evidenced that monoparental (ie., single mother) rearing condition in C57BL/6 mice induced an anxiety-like behavior and major alcohol consumption in adolescent offspring. Here, we aimed to analyze if mono- or biparental conditions could alter alcohol-induced locomotor stimulation and its effects on neural activation in several brain areas. Infant mice

were reared in a monoparental (MP, single mother) or biparental (BP, father and mother) condition. At postnatal days (PD) 16, 17, 18 and 20, infants were administered with a 0.0 or 2.0 g/kg alcohol dose and evaluated in an open field test. After, immunoreactivity to ΔFosB transcription factor, was analyzed in several brain areas. ΔFosB accumulates to high levels in brain after chronic stimulation and can be influenced by drugs exposure but also by natural rewarding stimuli. Finally, cathecolaminergic activity (ΔFosB/tyrosine-hydroxilase) was measured in ventral tegmental area. Results indicate that all animals were sensitive to alcohol-induced motor stimulation. MP-animals showed tolerance to this effect since PD17. Nevertheless, BP animals did not show tolerance even after the four days of test. Moreover, the intensity of this alcohol effect was more robust in BP than MP infants. A greater ΔFosB/TH-ir was observed in VTA in all alcohol-treated animals. Of major interest, MP-infants showed greater ΔFosB-ir in basolateral and central (CEA) amygdala, and this effect was exacerbated by alcohol in CEA' MP-infants.

In conclusion, BP-infants were more sensitive to alcohol-induced motor stimulation. On the other hand, MP-offspring showed greater activation in brain areas related to anxiety behaviors as BLA and CEA, and were more sensitive to alcohol effects in this last area. These results are in line to the previously reported anxious behavioral profile in MP-adolescents and highlighted the importance of social experiences during early development.

LONG-TERM FETAL DEVELOMENTAL ALTERATIONS AND CARDIOPATHY ASSOCIATED WITH OXIDATIVE STRESS INDUCED AFTER PERIGESTATIONAL ALCOHOL CONSUMPTION UP TO ORGANOGENESIS, IN MOUSE.

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Previously, perigestational moderate alcohol consumption up to organogenesis (day 10 of mouse gestation (D10), produces abnormal embryos with high apoptosis, diminished proliferation and altered myocardial embryonic wall. The present study assessed the effects of perigestational alcohol intake up to D10 and alcohol deprivation up to D13, on fetal development, cardiac histology, ultrastructure, proliferation and apoptosis and oxidative status. Ethanol 10% in drinking water was administered to murine CF-1 females for 15 days before and up to D10, and gestation continued with water until D13 (treated females (TF)). Control females (CF) were administered with drinking water without ethanol. TF consumed 18 g/kg/day, resulting in 25% EDC. Perigestational alcohol administration up to D10 did not affect differentiation and growth of D13-fetuses, but produced high frequency of abnormal fetuses compared to CF (27% vs 3.5 %, $p < .001$). The fetal cardiac wall thickness was reduced ($p < .001$, *Image J*) in 79% TF-fetuses compared to 13% of CF-fetuses. Hearts of TF-fetuses had diminished proliferation (Ki67, immunohistochemistry (IHC) ($p < .05$ vs controls), disorganized cardiomyocytic myofilaments and mitochondrial reduced size ($p < .01$) (transmission electronic microscopy) compared to CF-fetuses. The TF-cardiac tissues presented elevated

3 nitrotirosyne protein expression ($p < .01$, IHC), increased activated caspase-3 /1000 μm2 cell number ($p < .05$) and increment of lipoperoxidation (nmol MDA /mg tissue, TBARS, $p < .05$), compared to controls. Without changes in catalase, the SOD activity significantly increased in TF-fetuses ($p < .05$, vs CF). Dissected hearts from TF-fetuses had increased NADPHdiaphorase reaction *in toto* (*Image J*-densitometry) compared to CF ($p < .05$), revealing increased nitric oxide synthase activity. In conclusion, perigestational alcohol consumption, despite the cessation of alcohol intake at D10, induced D13-fetal cardiopathy by triggering long-term oxidative stress and leading to macromolecular damages in the exposed fetal tissues, suggesting that typical congenital cardiopathy of the Fetal Alcohol Spectrum Disorder may be originated after aternal alcohol ingestion up to early organogenesis.

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BELIEFS ABOUT ALCOHOL IN HIGH SCHOOL STUDENTS FROM THE METROPOLITAN AREA OF MONTEVIDEO (URUGUAY)

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The factors that stimulate alcohol consumption in Uruguayan youth are largely unknown. A study was conducted to gain perspective on the beliefs of adolescents and youngsters from Uruguay, a South American country with a relative large alcohol consumption per capita, regarding alcohol consumption and effects. A survey was applied to 296 high school students (53% male) inquiring about alcohol consumption beliefs. About a quarter (23%) indicated they believe alcohol is not an addictive drug whereas 61% classify alcohol as a depressive drug. Moreover, 25% and 60% believe peers and family, respectively, do not exert a significant influence on alcohol consumption. When asked about risk factors for alcohol consumption 33% indicated that adolescents possess higher tolerance to alcohol than adults do, and 48% disregard the possibility of sex-based differences in alcohol tolerance. They consider that alcohol can be consumed up to 5 days per month without compromising health processes. Similarly, they attest that 4,2±3,9 glasses of beer or 3,6±5,9 glasses of wine is the maximal amount that can be ingested in a single occasion without negative consequences. ANOVAs conducted on these indices indicated significant differences between those who believe that adolescents have higher alcohol tolerance than adults In addition, the men believe to possess higher tolerance levels per episode than women. These results contribute to the understanding of the beliefs held by Uruguayan high school students concerning alcohol consumption. This knowledge will be valuable for the design of prevention and screening efforts.

EFFECTS OF MONO- OR BIPARENTAL REARING ON PARENTS' BEHAVIORAL PROFILE, PARTNER PREFERENCE AND ALCOHOL CONSUMPTION

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We have previously reported that monoparental (MP) (ie., single mother) rearing condition in C57BL/6 mice implies that pups are more time unattended during the first postnatal weeks, when compared with biparental (BP) rearing. Also, MP-reared adolescents, show greater anxiety-like behaviors and major alcohol consumption. Here, we aimed to analyze if mono- or biparental rearing may affects parents' behavior, partner preference after cohabitation and alcohol consumption. After 4-5 months of biparental (mother-father) or monoparental (single mother) rearing condition, adults' parents and virgin males and females were evaluated in the concentric square field (CSF). Later adults' parents were evaluated for partner preference in the three-chambered social approach task for mice (TCST). Finally, parents and virgin animals were tested in a 4-hr daily, double-bottle alcohol consumption test (10% alcohol vs. water) during four weeks, three days per week. CSF results indicated that virgin adults spent more time in a highly illuminated exposed-risk area (bridge) and less time in a secure dark area (shelter) than BP- or MP-adults. MP-adults were the ones more active during the test. Virgin animals spent also more time per visit in the bridge than the other groups. Data from the TCST evidenced that cohabitation and parenting in this strain of mice (BP-condition) did not induce monogamy in males: BP-males showed preference for strange female over the partner. BP- and MP-females evidenced no preference between a stranger and the partner male. Finally, virgin animals display higher alcohol consumption scores in comparison with the remaining groups. Together, these results seem to indicate that parenting attenuates risk-associated behaviors that could underlie the enhanced vulnerability to develop alcohol-use.

THE ASSOCIATION BETWEEN ALCOHOL, TOBACCO AND MARIJUANA USE AND RISK PERCEPTION IN COLLEGE STUDENTS

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Alcohol, tobacco and marijuana use are highly prevalent at college. Perception of the risks associated with substance use (i.e., perceived risk [PR]) modulates engagement in substance use. This study examined, in college students, the perceived risk of using alcohol, tobacco, and marijuana and its association with alcohol, tobacco and marijuana use. We also examined differences in PR as a function of exhibiting last-year tobacco or last-year marijuana use, and differences in the PR of using alcohol as a function of exhibiting binge drinking (≥ 4/5 standard drinks per drinking session, women/men, respectively). College students (n = 279, 75.6% women; M age = 23.02 ± 3.36) completed an online survey that measured quantity (alcohol, tobacco) and frequency (alcohol, tobacco and marijuana) of substance use within the previous month and

year and PR of using alcohol, tobacco and marijuana (e.g., "How much do you think people risk harming themselves [physically, in their health, or in other ways] if they: 1-smoke >10 cigarettes per day, 2-drink 4–5 standard drinks every weekend, 3-consume marijuana >1 per week?"). Lower PR was significantly associated with greater quantity (alcohol *rs* between -.12 and -.35; tobacco *rs* between -.16 and -.23) and frequency of substance use (alcohol *r* between -.14 and -.32; tobacco *r* between -.19 and -.26; marijuana *r* between .26 and .56). Last-year tobacco users and last-year marijuana users perceived the use of tobacco ($t_{(277)} = 4.52$; $p \leq .001$) or marijuana ($t_{(277)} = 11.56$; $p \leq .001$) as less risky than peers who did not report use of these substances. Binge drinkers perceived alcohol consumption as less risky than non-binge drinkers ($t_{(277)} = 4.41$; $p \leq .001$). Discussion: Overall, results showed a significant negative association between PR and substance use, that was particularly robust for marijuana. This information allows a better understanding of substance use in emerging adults, which should be useful to identify college students at-risk for problematic substance use.

MATERNAL ODOR INCREASES THE CONSUMPTION OF A SOLUTION THAT MIMICS BITTER AND SWEET COMPONENTS OF ETHANOL TASTE IN RATS

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Several studies showed that early exposure to ethanol increased the subsequent acceptance of this drug on rats. However, little attention has been devoted to the interaction between the alcohol's taste -isolated from the unconditioned effects of the drug- and a familiar odor in the early ontogeny of the rat. Studies from our laboratory showed that a familiar (maternal) odor increased the consumption behaviors toward an artificial nipple containing an unpalatable tastant (quinine) in newborn rats. The present study assessed the influence of the own mother's odor (familiar due pre-exposure in the nest) on intake and grasp responses toward an artificial nipple providing a solution with a mixture of tastes (sucrose 0.1 M + quinine 0.0001 M) that emulates the taste of alcohol, in 4-day old pups. The results showed that the mother's odor enhanced intake and seeking responses toward an artificial nipple that provided the solution that mimicked the taste of alcohol (Experiment 1). This pattern of results was not evoked by the odor of an unrelated dam, nor was observed when the nipple delivered water (Experiment 2). The main new finding of the present study is that animals tested in the presence of the mother (and hence exposed to its odor cues) exhibited enhanced seeking and intake of a solution that mimics the chemosensory properties of ethanol without the unconditioned effects of the drug. This suggests that, during the early ontogeny, the exposure to familiar odors may facilitate the acceptance of flavors with aversive components (i.e., bitter taste), and therefore may act as a permissive factor of ethanol intake.

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ALCOHOL PROTECTIVE BEHAVIORAL STRATEGIES IN ARGENTINEAN COLLEGE STUDENTS

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Protective behavioral strategies (PBS) reduce or minimize the negative consequences of alcohol drinking. Previous work, conducted mostly in the U.S., showed that PBS are negatively related to alcohol outcomes and that women exhibited greater use of PBS than men did. The Protective Behavioral Strategies Scale [PBSS] is one of the most used instruments to measure this variable. The present study examined PBS use (as measured by the Protective Behavioral Strategies Scale, PBSS) in 771 freshman college students (62.1% women, *M* age = 19.61±3.78) from Argentina, and its association with drinking indicators and alcohol-related negative consequences. College freshman that reported alcohol use within the previous month completed an online survey that assessed alcohol use (frequency, quantity, frequency of binge drinking/drunkenness episodes), alcohol-related negative consequences and PBS. Alcohol use was highly prevalent, with 27.1% of women and 40.8% of men reporting having drinking >5 days in the previous month, and 32% (women) to 42% (men) reporting drinking >4 standard drinks of alcohol per drinking session. Women reported significantly higher number of PBS (e.g., stopping drinking at a predetermined time, avoiding drinking games, leaving the party at a predetermined time) than men did ($t_{(769)} = 2.96$; $p \leq .01$). A greater use of PBS was, particularly among women and particularly those describing manners of, was significantly associated with lower alcohol use (i.e., frequency and quantity of alcohol use) and alcohol-related negative consequences. The present findings, which largely replicate those found in the U.S., suggest Argentinean college women exhibited greater use of PBS than men. Despite these sex differences, a greater use of PBS was significantly associated with lower alcohol use and less alcohol-related negative consequences in both, women and men. PBS hold promise as potential targets of interventions aimed at reducing alcohol use and its associated negative consequences.

NOISE EXPOSURE OF ADOLESCENT FEMALE RATS INDUCES HIPPOCAMPAL AMINOACIDERGIC NEUROTRANSMISSION CHANGES THAT CAN BE PREVENTED BY PRIOR ETHANOL INTAKE.

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Adolescence constitutes a critical period in the maturation of the Central Nervous System (CNS) and its normal development can be altered by the presence of harmful environmental factors. Ethanol is one of the chemical compounds most used for recreational purposes by human adolescents and it has the ability to affect the CNS. In addition, ethanol consumption usually occurs in the presence of high noise intensities in different entertainment places. Therefore, the use of an animal model of ethanol intake combined with noise exposure could be clinically relevant. We have previously demonstrated that rats exposed to noise at

childhood can induce hippocampal (HC)- related behavioral and biochemical alterations, including changes in aminoacidergic neurotransmission. In consequence, the aim of the present work was to investigate possible changes that voluntary ethanol intake in conjunction with noise exposure during early adolescence might induce on hippocampal aminoacidergic neurotransmission. Female Wistar rats (28-days-old) were subjected to 10% ethanol or 1% sucrose using the two-bottle choice drinking in the dark paradigm, during 4h/day for 4 days. After last session, animals were exposed to noise (95-97 dB, 2h) and HC tissue was dissected for Western Blot experiments to evaluate the levels of GAD 65/67 (a marker of GABAergic neurotransmission) and EAAT-1 (Excitatory amino acid transporter 1, a marker of glutamatergic neurotransmission). Results showed no significant changes on GAD 65/67 enzyme and EAAT-1 multimers levels between either groups. However, a decrease in glycosylated EAAT-1 was found in animals exposed to noise, which was prevented on animals that consumed alcohol before noise exposure. Glycosylated EAAT-1 is important for the generation of the active multimeric forms and for the extra-cellular expression of other glutamate transporters. Therefore, considering that glutamate transporters play a crucial role in the removal of the excess of glutamate to limit its neurotoxic effects, the observed decrease in glycosylated EAAT-1 could lead to difficulties in preventing harmful glutamate increase, especially if the individual is being continuously exposed to pro-excitotoxic agents. Finally, these findings suggest that exposure to physical and chemical agents during adolescence could induce HC-related biochemical alterations, demonstrating a high vulnerability of the developing brain.

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ALCOHOL MIXED WITH ENERGY DRINKS (AMED) INCREASES THE RISK OF DRINKING PROBLEMS IN HUMANS

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The use of energy drinks associated with alcoholic beverages is very popular, specially among young people. In previous studies, in mice, we demonstrated this mixture increases the sensitization to the stimulant effect of ethanol as well as the proportion of animals which develop sensitization. In studies with volunteers we demonstrated energy drinks reduced the subjective perception of alcohol intoxication, but they did not reduce the negative effects of alcohol on motor coordination tests. Although there some studies about the use of AMED by college students indicating it has been associated with at-risk use of alcohol, we did not find studies comparing sporadic with frequent users of AMED, which was the purpose of the present study. We analyzed data from 937 people on their consumption of alcohol and energy drinks collected through a self-administered online questionnaire, using Google Forms platform. Based on the answers to the screening test AUDIT and on the questions about the frequency of use of AMED, we classified the users as frequent (34.7%) or sporadic (65.3%) AMED users and in the four zones of risk of AUDIT. We compared their frequency of associated problems, specially the binge drinking frequency. In the frequent users of AMED the report of alcohol-related problems (zones 3 and 4 of AUDIT= 51.6%) and binge drinking (58.4%) was significantly higher than among sporadic users (respectively, 29% and 39.1%).

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ALCOHOL-RELATED NEGATIVE CONSEQUENCES IN URUGUAYAN YOUTH.

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The assessment of alcohol-related negative consequences is important to understand the impact of alcohol use in specific populations and for the design of public policies. This work assessed the main consequences of alcohol consumption in Uruguayan youth. A survey applied the Young Adult Alcohol Consequences Questionnaire (YAACQ) in 1505 youth, aged between 18 and 30 years (25% men, Mean age = 23.5 ± 3.5 years). The scale assessed, in 6 subdomains, the main consequences of alcohol consumption in the last 6 months. The main consequences reported were to wake up with a hangover the day after drinking (67%), drinking more than originally planned (54%), engaging in shameful activities (50%), throwing up (48%), and experimenting memory blackouts (33%). The frequency of consequences was negatively associated with age (r = -0.08, $p < .05$), and men reported more negative consequences than women ($p < .05$). In addition, more consequences were seen in participants from Montevideo than In those from the rest of the country, whereas no differences were found between college students and non-college students. This information is useful for design interventions of and public policies aimed at young people.

GELATINASES AS MARKERS OF CHRONIC ALCOHOL CONSUMPTION: A PILOT STUDY IN URUGUAY.

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Chronic alcohol consumption in Uruguay is a growing problem, however, determinations of consensual biomarker are not performed systematically neither potential new markers are explored. To validate the hypothesis that matrix metalloproteinases (MMPs) with gelatinase activity are biomarkers of chronic alcohol consumption, samples of 100 alcoholics that began medical treatment at the Unidad de Trastornos Relacionados con el Alcohol (UNITRA) and 50 healthy non-alcoholic donors were evaluated. Alcoholic samples showed gelatinase activity that tripled that of controls and small but significant increases in levels of gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST) and mean cellular volume (MCV). Carbohydrate deficient transferrin (CDT) values were lower in alcoholics than in controls. These results allow proposing gelatinases as the most sensitive indicators of sustained alcohol consumption in the population analyzed since hepatic enzymes and mean cellular volume showed a tendency consistent with the literature

but did not reach values associated with the pathology. Since carbohydrate-deficient transferrin is considered the most sensitive and specific indirect biomarker of chronic alcohol consumption, data obtained indicating lower values in alcoholics than in controls suggest methodological problems that could be solved by applying other measurement techniques. Finally, these findings justify an extension of this pilot work, as well as additional studies focused on the participation of matrix metalloproteinases with gelatinase activity in the cascades of damage associated with chronic alcohol consumption.

MICE PATERNAL ALCOHOL EXPOSURE AFFECTS EPIGENETICS MARKS ON SPERM ALTERING THE TESTIS STRUCTURE FROM ITS OFFSPRING

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Previously, we observed that male alcohol consumption increased the sperm rate of decondensation, delayed embryo differentiation by deregulating peri-implantation events and altering embryo trophoblast and inner cell mass morphology *in vitro*. This study evaluates the effect of paternal alcohol consumption on spermatozoa and testis and its effect on male offspring. CF-1 male mice were exposed (treated group, T) or not (control group, C) to 15% (v/v) ethanol in drinking water *ad libitum* for 15 days. Sperm from epididymal cauda were obtained by swim-out to determine sperm oxidative stress with the *CellROX Green* Flow Cytometry Assay Kit and epigenetic marks of histone for immunocytochemistry. Testicles were weighted and the DNA fragmentation was analyzed by TUNEL assay on both groups. Males from control and treated groups were mated with non-treated CF-1 female mice in a ratio 1:1. Sperm from cauda of adult male mice of the offspring (F1) were obtained by swim-out to determine sperm parameters and head decondensation. Testicles of F1 mice were weighted and analyzed histologically. Male alcohol consumption did not alter testicular weight but increased sperm oxidative stress (fluorescence intensity: 2.2 ± 0.2 $n = 5$ C vs 3.0 ± 0.2 $n = 4$ T, $p < .01$) On the other side, we observed a significant decrease of epigenetic marks of histone H3K4me3 in sperm from T group compared to C group (positive mark: 7.0 ± 3.7 $n = 8$ T vs 27.1 ± 8.2 $n = 11$ C, $p < .05$). Besides, we detected an increment of TUNEL labeling on germinal line from testicles of treated groups vs. control groups (56% ± 6% T vs 21% ± 4% C, $p < .01$, $n = 2$). When we analyzed F1 mice we could detect differences in the testicles weight (0.099 ± 0.004 g $n = 11$ T vs 0.118 ± 0.006 g $n = 11$ C, $p < .05$) and their germinal line thickness from F1 male mice of treated group (275 ± 3 μm, $n = 7$ C vs 249 ± 8 μm, $n = 5$ T, $p < .01$) being both significantly minor that those in control group. However, there were not differences in sperm concentration, motility and head decondensation between both groups of F1 male mice. Taking together, these results suggest that short-term paternal alcohol consumption impairs epididymal sperm quality altering the male reproductive biology and inheriting reproductive defects to their male offspring.

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DIFFERENCES IN MARIJUANA OUTCOMES AS A FUNCTION OF SEX AND FREQUENCY OF USE

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Marijuana is the most extensively used regulated drug in the world. Prevalence of marijuana use peak in emerging adulthood and, particularly, during college years. Heavy marijuana use is associated with a broad myriad of negative consequences (lower academic achievement, increased rate of dropout, risky sexual behavior). Traditionally, men have exhibited a greater prevalence of marijuana use than women. The present study examined the occurrence of marijuana use and marijuana-related negative consequences (NC) in a sample of Argentinean college students (n = 279, 75.6% women; M age = 23.02 ± 3.36 years). Specifically, we examined 1-differences in marijuana outcomes (i.e., prevalence and NC) as a function of sex and 2-differences in NC between high- and low-frequency users. Participants completed an online survey that measured frequency of marijuana use during the previous year and month and NC (assessed with the Marijuana Consequences Questionnaire [MACQ]). The MACQ is a 50-items scale grouped in eight subscales: Social-interpersonal Consequences, Impaired Control, Self-Perception, Self-Care, Risk Behaviors, Academic/Occupational Consequences, Physical Dependence, and Blackouts. Each item is scored dichotomously to reflect presence/absence of the NC. The total score reflects the total number of NC. We conducted X^2 tests to examine the association between sex and prevalence of marijuana use. We applied the Student's t-test to examine differences in NC as a function of sex and frequency of marijuana use. Results: Marijuana use was highly prevalent with 46.6% and 33% exhibiting last year and last month use, respectively. Men and woman exhibited a statistically similar frequency of marijuana use. Findings suggest that men and women exhibited statistically similar NC in all, but self-perception ($t = 2.26_{(128)}$; $p \leq .05$; men more NC), MACQ's subscales. High-frequency, compared to low-frequency, users experienced a significantly higher quantity of NC in Impaired Control, Self-Perception, Self-Care, Academic/Occupational Consequences, and Physical Dependence. Discussion: The present findings suggest that frequency of marijuana use is similar between men and women; however, those students who reported higher frequency of marijuana use experienced a significantly higher number of NC. This information is relevant for early detection and/or intervention targeting college students at risk for developing problems associated with marijuana use.

ELSA 2016 COHORT: ASSOCIATION BETWEEN EARLY ALCOHOL, TOBACCO, OR MARIJUANA USE AND SUBSTANCE USE IN ARGENTINEAN COLLEGE FRESHMEN.

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Earlier alcohol, tobacco, or marijuana consumption is associated with a greater risk of developing drug-related problems, including substance use disorders. Some authors have postulated that this risk is substance-specific (i.e., early alcohol use leads to alcohol- but not marijuana-related problems). Other authors have suggested a broader effect, in which the initiation of use of any substance (e.g., alcohol or tobacco) heightens the risk of using these and other psychoactive substances. The present study examined, in a large sample (n = 4083; 40.1% men; mean age = 19.39 ± 2.18 years) of Argentinean college freshmen, the association between age of onset (early, late) of alcohol, tobacco, and marijuana use and different indicators of substance use. Participants completed a survey that measured age of onset of alcohol, tobacco and marijuana use and different indicators of use (for each substance). The effect of age of first use on substance use was analyzed separately for each substance using the χ^2 test or Student's t-test for nominal and continuous dependent variables, respectively. These analyses were conducted in the subsample that had reported lifetime use of each substance. Results: Overall, results showed that the onset of alcohol use preceded the use of tobacco, which, in turn, preceded the use of marijuana. We identified substance-specific associations: early use of alcohol, tobacco, and marijuana was associated with a higher likelihood of consuming each of these substances. Despite this, an early drinking onset was significantly associated with a greater occurrence of all indicators of tobacco and marijuana use. Moreover, the effect sizes of the associations between early drinking onset and subsequent use of all three substances were larger than the effect of early tobacco or marihuana use on subsequent use of these substances. Discussion: Altogether, our findings suggested that alcohol was the entry-point substance for the majority of the participants and a broader effect of alcohol initiation that heightens the risk of consuming alcohol and using other substances. The findings suggest that programs directed toward delaying the onset of alcohol use may be particularly useful among these individuals.

SOCIOECONOMIC INEQUALITIES IN ALCOHOL CONSUMPTION IN ARGENTINA: COMPARATIVE ANALYSIS 2009–2013

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Research on socioeconomic inequalities in alcohol use has been a topic of increasing concern but not sufficiently understood. Traditionally, research about social inequalities in health suggests that individuals with lower socioeconomic status (SES) have poorer health than those who belong to higher socioeconomic groups (Dalstra, 2006). In regard to alcohol consumption there is sufficient evidence that is concentrated among more

favored individuals. Although lower socioeconomic groups exhibit higher rates of abstinence, heavy drinking is more prevalent among these individuals (Bloomfield et. Al, 2006). Low and middle income countries might present different patterns than developed countries. There is some evidence from Brazil showing that higher socioeconomic status is strongly associated with high risk drinking (Almeida-Filho, 2005). In Chile no socioeconomic gradient was found in heavy episodic drinking (HED), whereas heavy volume drinking is concentrated among higher SES individuals (Peña et al, 2017). There is a lack of enough evidence about SES inequalities in alcohol consumption in Argentina. The present study analyses SES inequalities in alcohol consumption and harmful use of alcohol in Argentina. Using data from National Survey of Risk Factors, waves 2009 and 2013, concentration indices (CI) are calculated for monthly prevalence and HED. The monthly prevalence shows a strong socioeconomic gradient, since the highest income quintile concentrates the biggest proportion of consumers in both periods. It is noticeable that the proportion of consumers in the lowest quintile is significantly higher in 2013 than in 2009. The CI for the total sample in both waves are statistically significant and greater than zero, showing that monthly prevalence is concentrated in higher SES individuals. This result indicates that alcohol is a "normal good", since its consumption grows with the per capita household income level. In regard with HED, it increased throughout all age groups and income levels, between the two waves. The highest HED prevalence is found in the 18-34 aged group. In spite the CI for HED for the total sample in both waves are pro-poor, CI for subsamples reveal a different pattern of inequality in 2013 respect 2009: HED is pro-rich among young people aged 18-34 living in larger cities, while CI is still pro-poor for the rest. This result contrasts with Peña et al. 2017, and suggest the convenience of targeted alcohol interventions.

ASSESMENT OF COGNITIVE EFFECTS OF BINGE DRINKING AT ADOLESCENCE AND ADULHOOD IN RATS

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Binge drinking is a widespread behavior. A recent study reported that close to 60% of a sample of college students from Argentina consumed 4-5 drinks in 2 ≤ hours. These consumption patterns can yield short- and long-term negative consequences, including cognitive alterations. We study the effects of binge ethanol exposure during adolescence (postnatal days 30 to 60, PDs 30-60) or young adulthood (PDs 70-100) on anxiety response, exploration of novel environments and short-term memory. Specifically, we exposed adolescent or adult rats to self-administered (concentration: 8-10%) ethanol during the first two hours of the dark cycle, every other day for four weeks; or the rats were given only handling (control group) or were administered ethanol (i.p.) at doses that matched those ingested by the rats in the self-administration group. The rats were then tested in the light-dark box test (LDB), in an open field (OF) test and in a novel object recognition (NOR) test. The results indicated greater anxiety response in the LDB in male adolescent, but not in male adult, rats given binge or i.p. ethanol, relative to non-exposed controls. Adolescent, but not adult, rats exposed to self-administered binge ethanol exhibited heightened motor habituation during the open field assessment and more time spent interacting with the objects introduced in the arena during the NOR test. Level of short-term recognition memory, however, was similar across age, sex and history of ethanol

exposure. The present results highlight some subtle, yet relevant, behavioral impairments induced by binge ethanol exposure. A relevant finding is that these alterations were observed when the binge ethanol exposure occurred at adolescence, but not when the exposure occurred at adulthood.

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INFLUENCE OF HIGH-FAT DIET WITHDRAWAL IN THE ETHANOL PREFERENCE AND ITS RELATION ON MOLECULAR MECHANISMS OF REWARD SYSTEM

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Studies describe that obese subjects and individuals with alcohol use disorder present behavior similarities, since both hypercaloric diet consumption and alcohol intake seems to activate the mesocorticolimbic dopaminergic pathway involved in reward and motivational processes. Unfortunately, most reports studied the relation of hypercaloric diet and ethanol consumption in animal models of intermittent or short periods of high-fat diet accesses, without considering the effects of chronic consumption and withdrawal on ethanol intake. Here, we describe an animal model to study how chronic high sugar and butter (HSB) diet and its withdrawal influence alcohol intake and anxiety behavior, as well as transcriptional regulation of dopaminergic and GABAergic receptors in two brain regions of reward system, Nucleus Accumbens (NAc) and Prefrontal Cortex (PFC). In the first stage (T1) fifty-eight C57BL/6JUnib male mice were fed on standard (AIN93G) or HSB diet for 8 weeks. Then, a protocol of free-choice between water and a 10% alcohol solution was introduced for the next 4 weeks (T2), and HSB diet was replaced with AIN93G in two (HSB-AIN93G+H2O and HSB-AIN93G+EtOH) of six experimental groups (AIN93G+H2O, AIN93G+EtOH, HSB+H2O, HSB+EtOH). At end of T1 and T2 animals were subjected to a Marble Burying test. Our results indicate that 8 weeks of HSB diet induced weight gain and significant accumulation in fat tissue that was associated with metabolic dysfunction, besides triggered behavioral changes, due to altered burial behavior. Additionally, HSB diet withdrawal led HSB-AIN93G+EtOH animals to drink more ethanol in comparison with AIN93G+EtOH and HSB+EtOH. Transcriptional regulation showed a differential regulation for dopaminergic receptor (Drd1 and Drd2) and GABAergic receptor genes (Gabbr1 and Gabbr2) in the NAc and PFC, respectively. These imbalances could drive the increase of alcohol preference and consumption during HSB diet withdrawal in HSB-AIN93G+EtOH mice. Our model shows a relationship between high-fat diet consumption and alcohol intake that appears to depend on the presence or absence a diet when alcohol intake is evaluated and confirm that diets rich in fat can activate the same brain circuits that are activated by some drugs of abuse.

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EFFECTS OF PRENATAL ETHANOL EXPOSURE ON EXPLORATORY AND ANXIETY-LIKE BEHAVIOR AND SOCIAL INTERACTION

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The aim of the present work was to analyze the effect of prenatal binge-like ethanol exposure to a moderate dose (2.0 g/kg; group Pre-EtOH) during the gestational days 17 to 20 on exploratory and anxiety-like behavior and social interaction of adolescent offspring (postnatal day 28-33). Pre-EtOH rats exhibited hypolocomotion in the open field test, showing a significant less distance travelled than control group (Mean = 87.6 ± 5.36). This effect was also evident when only the center area of the open field was taken into account (Mean = 6.85 ± 0.73). No significant differences could be observed for time spent in the center of the chamber. A significantly lower number of rearing behavior was also evidenced (Mean = 22.92 ± 1.79) in Pre-EtOH animals and in males adolescents, but the interaction of the factors did not attached significance. In the elevated plus maze, the time spent on the closed arms (Mean = 255.75 ± 11.1) and time spent in open arms (Mean = 8.84, 92) were significantly different as a function of prenatal treatment. PreEtOH group spent more time in closed arms than control. Head dipping behavior was also significantly lower in PreEtOH than control group (Mean = 2.4 ± 0.5). The analysis of behavior in the three-chamber social interaction test did not show any significant differences in the interaction with a new congener or objet between the control and Pre-EtOH group. In conclusion, the prenatal binge-like exposure to a moderate ethanol dose reduced exploratory motor activity and increased anxiety-like behavior during adolescence. However, the Pre-EtOH exposure did not seems to affect social interaction with novel congeners at this age.

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