

Posters

Involvement of dorsal hippocampus in context-induced the reinstatement of ethanol-seeking behavior in C57BL/6 mice

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ABSTRACT

The ABA renewal is an important animal model to study the influence of contextual cues on the reinstatement of ethanol-seeking. Here, we standardized a protocol for context-induced reinstatement of ethanol seeking in mice and investigated the involvement of the dorsal hippocampus in this behavior. For that, male C57BL/6 mice, at 8-10 weeks of age, were given free access to either a 9% ethanol + 2% saccharin (ES) or a 2% saccharin solution (SA) and water in their home cage, followed by an involuntary four-hour consumption of these solutions. Then, mice were trained to self-administer ES or SA in context A during three sessions of 16h, followed by 15 sessions of 1h. We extinguished drug-reinforced responding in a distinct context B for 14 sessions and assessed context-induced reinstatement of the alcohol-seeking behavior by placing the animals in context A or B. Sixty min later, mice were perfused, and brains were removed for immunofluorescence analysis for

Fos (cell activation marker) and NeuN (neuron marker) in the dorsal hippocampus. We found that animals of both groups acquired the operant self-administration behavior in context A and extinguished this behavior in context B. Re-exposure to context A but not context B reinstated the seeking behavior and increased neuronal activation in the hippocampal CA1 and CA2 regions in ethanol and saccharin groups. Thus, our findings suggest that the association of ethanol with saccharin facilitated the establishment of context-induced reinstatement protocol, and the context induced reinstatement of ethanol seeking is associated with the activation of CA1 and CA2 hippocampal subregions.

Keywords: ethanol, renewal, mice, hippocampus

Rats who lives with depressed ones drink more alcohol

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ABSTRACT

An interesting phenomenon, emotional contagion, allows the transmission of emotional states and, along with this, of behavioral patterns from one individual to another. The aim of our work was to observe the influence of emotional contagion on alcohol consumption in euthymic rats that cohabit with pharmacologically depressed peers. 40 female adolescent Wistar rats were used, which were divided into 5 boxes, designating one box as control.

In the remaining 4 boxes, 6 animals were depressed using reserpine (a monoamine depletor) and the other two animals (socials), as well as the controls, were only administered physiological solution. Behavior tests (Open Field and Light/Dark Box) were performed on days 20, 40 and 60 of cohabitation in order to assess the existence of emotional contagion. The test's results confirm emotional contagion effects. After a period of coexistence of 60 days, 8 sessions of alcohol consumption (5% ethanol) and 2 of water intake were carried out every 24 hours. The data obtained show that the social animals consumed significantly more alcohol than controls in sessions 4 and 7 ($p < 0.05$). The increase in consumption corresponding to day 4 shows a greater resistance to the aversive effects of the drug, while the increase on day 7 shows a greater reinforcing effect of alcohol. Data show that emotional contagion could influence alcohol consumption in rats.

Keywords: alcohol, emotional contagion, rats, Wistar

Effect of HCN2 inhibition in the ethanol-induced dopamine release in the Nucleus Accumbens of rats.

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ABSTRACT

The mesocorticolimbic system is a primal neuronal pathway involved in the reinforcement of survival natural rewards. This system is conformed to dopaminergic neurons that project their axons from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) and other structures. Ethanol and other abused drugs can activate the dopaminergic activity of the mesocorticolimbic system, which

translate into an increase in the release of dopamine in NAc. HCN2 ion channels (Hyperpolarization-activated cyclic nucleotide-gated) are responsible for pacemaker activity of dopaminergic neurons in the sinoatrial node and VTA. This channel has four isoforms (HCN1-4), HCN4 is the main isoform in the heart, and HCN2 is the most abundant isoform in VTA. Recent studies in our laboratory suggest that HCN2 ion channels are involved in alcohol rewarding effects since when HCN2 was overexpressed or silenced in VTA, an increase or a reduction in alcohol consumption was observed. ZD7288, MEL55A, and 4e are pharmacological inhibitors of HCN, each with a different affinity for HCN2, with 4e being the most selective, but they are never tested in an alcohol preclinical setting. In this work, we will synthesize 4e, and evaluate the ethanol-induced dopamine release in NAc, when a dose from HCN inhibitor (ZD7288, MEL55A, or 4e) is administrated in the cerebral ventricle. The dopamine levels will be measured by microdialysis in vivo coupled to HPLC/electrochemical detection. We hypothesize that these inhibitors will block the dopamine increase in the NAc upon the administration of a systemic dose of ethanol.

Keywords: alcoholism, dopamine, mesocorticolimbic system, microdialysis, HCN ion channels, synthesis

A new drug that decreases both alcohol consumption and ethanol-induced neuroinflammation.

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ABSTRACT

High-ethanol intake induces a neuroinflammatory response, which has been proposed as responsible

for the maintenance of chronic ethanol consumption. Neuroinflammation decreases glutamate transporter (GLT-1) expression, increasing levels of glutamate that trigger dopamine release at the corticolimbic reward areas, driving long-term drinking behavior. The activation of PPAR α by fibrate drugs inhibits neuroinflammation, in models other than ethanol consumption. However, the effect of fibrates on ethanol-induced neuroinflammation has not been studied. We previously reported that the administration of fenofibrate to ethanol-drinking rats decreased ethanol consumption. Here, we studied whether fenofibrate effects are related to a decrease in ethanol-induced neuroinflammation and to the normalization of the glutamate transporter (GLT-1). The levels of GFAP, plkB α , TNF α , IL-1 β , IL-6, IL-10 and GLT-1 were quantified in the prefrontal cortex, hippocampus, and hypothalamus. Ethanol treatment increased the levels of GFAP, plkB α and all the inflammatory cytokines, while the administration of fenofibrate normalized these increases. These results indicate that fenofibrate reverts neuroinflammation probably through the inhibition of NF- κ B. Finally, ethanol decreased GLT-1 expression in the prefrontal cortex and hippocampus. Fenofibrate normalized the levels of GLT-1 in both areas, suggesting that its effect in reducing ethanol consumption could be due to the normalization of glutamatergic tone.

Keywords: neuroinflammation, glutamate transporter, fibrates

Effect of epigenetic changes in the nociceptin system caused by maternal separation stress on ethanol consumption in mice.

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ABSTRACT

Early stress exposure can increase the vulnerability of the individual to develop Alcohol Use Disorder in adulthood. Although relevant, the neurobiology of this interaction remains unclear. Studies indicate the involvement of nociceptin in the stress-induced increase in ethanol consumption. Stress can also promote changes in epigenetic mechanisms related to alcohol consumption. We evaluated whether maternal separation stress could promote epigenetic alterations in the nociceptin system and whether these changes would be correlated with an increase in ethanol intake in adulthood. C7BL/6J mice were separated from the dam (maternal separation, MS) 3h/day, from PND (postnatal day) 1 to PND 14. Starting at PND 60, animals had access to ethanol solution or water 8h/day. Ethanol concentration increased each 3 days (5%, 10%, 15%, 20% w/v). Later, animals underwent three days of abstinence, followed by a re-exposure to 20% alcohol and water. Brains were collected, and epigenetic marker levels in the amygdala and the bed nucleus of stria terminalis (BNST) were assessed by Western Blotting. Next, distinct groups of mice received sodium butyrate, decitabine, or vehicle intraperitoneal injections during the abstinence period, and the expression of nociceptin and its receptor was assessed by RT PCR. It was found that: MS increased ethanol consumption and preference in adulthood; MS did not change the levels of acetylated histones, histones 3 di-methylated in lysine 9, Sirtuin-1 and DNMT1 in BNST or amygdala; Sodium butyrate or decitabine administration did not modify ethanol consumption nor nociceptin and NOP mRNA levels in the BNST; MS reduced the NOP expression in BNST. Our findings demonstrate the long-term consequences of MS on alcohol intake, suggesting early life stress as a risk factor for alcohol abuse.

Keywords: maternal separation, alcohol, intake, PCR

Role of basolateral amygdala neuronal ensembles in context-induced reinstatement of ethanol seeking

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ABSTRACT

Contextual cues previously associated with drug use often provoke relapse to drug use in humans and reinstatement of drug-seeking in laboratory animals. Considering the role of amygdala in encoding conditioned drug-related memories, the present study examined whether context induced ethanol-seeking is mediated by the activation of neuronal ensembles of the basolateral amygdala (BLA). To assess a causal role for the BLA neuronal ensembles in context induced reinstatement of alcohol seeking, we used the Daun02 inactivation procedure to selectively inactivate these neurons. We trained c-fos-lacZ transgenic rats to self-administer ethanol in Context A and extinguished their lever-pressing in Context B. On induction day, we exposed rats to either Context A or a novel Context C for 30min and injected Daun02 or vehicle into BLA 60min later. After three days, we performed the reinstatement test. The ability of Context A to reinstate ethanol seeking was attenuated when Daun02 was previously injected after the induction on Context A (number of active lever presses: 15.6±4.5 vehicle (n=10), 9.2±2.9 Daun02 (n=9)). However, Daun02 injections after exposure to Context C had no effect on context induced reinstatement of ethanol seeking (number of active lever presses: 9.1±3 vehicle (n=8), 11±5.6 Daun02 (n=9)). Our data suggest that context-induced reinstatement of ethanol seeking is mediated by activation of context-selected BLA neuronal ensembles.

Keywords: alcohol; amygdala; c-fos-lacZ; Daun02; renewal

Involvement of CRFergic neurotransmission in the long-term effects of maternal separation on alcohol intake of male and female mice after an acute stress exposure

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ABSTRACT

Maternal separation (MS) stress protocol is a predictive animal model to assess the effects of early stress exposure on alcohol intake. However, the underlying neurobiological mechanisms involved in the interaction between Alcohol Use Disorders (AUD) and stress are not fully understood. We aimed to investigate the influence of MS on alcohol consumption and the involvement of CRFergic neurotransmission after an acute heterotypic stressor exposure during adulthood. C57BL/6J mice were subjected to 180 min of MS from postnatal day (PND) 1 to 14 or were left undisturbed in their home cage (control). On PND 45, mice were exposed to 20% alcohol (w/v) in filtered water in their home cages for three weeks (involuntary consumption). Next, mice were trained to self-administer alcohol in an operant procedure under a fixed ratio (FR 1-3-5), 120-min sessions. The “breakpoint” was determined in 3 two-hour sessions of a progressive ratio schedule. The next day, mice were submitted or not to Rat Exposure Test (RET). After 24h, they had free access to 20% alcohol for four hours (binge). Bed Nucleus of Stria Terminalis (BNST) and Amygdala (AMY) were

collected for Western Blotting. In involuntary consumption, female mice increased alcohol intake compared to male mice. Male mice submitted to RET increased the number of reinforcements in the binge. CRFR1 receptors expression decreased in BNST of MS mice not submitted to RET, and CRF binding protein expression increased in their AMY. MS mice submitted to RET expressed more CRFR2 receptors than control mice. MS stress seems to influence CRFergic neurotransmission after an acute heterotypic stressor exposure in adult mice.

Keywords: alcohol use disorders, maternal separation stress, alcohol operant self-administration, Corticotropin Releasing Factor.

Prospective and reciprocal effects of alcohol use and impulsivity among adolescents in Argentina

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ABSTRACT

Alcohol use and impulsivity exhibit a complex relationship. Alcohol use can promote impulsive behavior, yet those with higher impulsive traits are more likely to engage in alcohol use, especially hazardous alcohol use. This longitudinal study examined the bidirectional relationship between alcohol use and impulsivity in Argentinean adolescents. High school students ($N=793$, $M=12.45\pm 0.93$; 55% women) reported last-year frequency of alcohol use and completed the Impulsivity UPPS-P Scale (5 dimensions: Positive [POS URG] and Negative Urgency [NEG URG], Sensation Seeking [SENS], Lack of Premeditation [PREM] and Lack of Perseverance [PERS]). Data

collection occurred in 3 time points (T1-T3), each wave 1 year apart. We conducted Cross-Lagged Panel Model analyses to examine reciprocal changes in alcohol use and impulsivity over time. We found that higher levels of (lack of) PERS predicted higher frequency of alcohol use at both timepoints (T2 and T3). Adolescents with higher levels of NEG URG and (lack of) PREM at T1 exhibited higher frequency of alcohol use at T2, whereas those with higher levels of POS URG and SENS at T2 showed higher alcohol use at T3. On the other hand, adolescents with higher frequency of alcohol use showed higher levels of NEG URG at T2 and T3 and higher levels of SENS at T2. Altogether, these results provide evidence that an impulsive personality can be a predictor of increases in alcohol use a year later, and that alcohol use can also predict later increases in impulsive personality. These findings can be useful for treatment and intervention efforts.

Keywords: alcohol, impulsivity, adolescence, longitudinal.

Folate administration at pregnancy ameliorates the facilitatory effects of prenatal ethanol exposure on postnatal ethanol intake

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ABSTRACT

Introduction: Prenatal ethanol exposure (PEE) is associated with numerous behavioral deficits and greater likelihood of ethanol intake at adolescence. The prenatal administration of folate is a promising approach to reduce the effects of PEE, albeit its impact is still under analysis. Objectives: We tested, in male and female Wistar rats, if prenatal folate administration modulated the effects of PEE on ethanol intake and preference. Methods: This experiment involved 119 adolescent Wistar rats derived from dams given folate (20 mg/kg, gestational days –GD- 13-20) + ethanol (2.0 g/kg, GD 17-20), ethanol or only vehicle at pregnancy. The offspring of these rats was tested for ethanol intake and percent preference vs. water, via two-bottle intake tests (length: 24 h), conducted on postnatal days (PDs) 28, 30, 35 and 36. Results: PEE significantly enhanced absolute and percent ethanol intake, when compared to the control group (i.e., rats given only vehicle). The rats given folate before PEE did not differ from controls. These effects suggest that folate inhibits the facilitatory effect of PEE upon (absolute and percent) ethanol intake at adolescence.

Keywords: folate, rat, prenatal ethanol exposure, alcohol, protective effects

Alcohol use in young adults: drinking motives and alcohol-related consequences

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ABSTRACT

High rates of alcohol consumption are observed among young adults, which is especially characterized by being excessive and episodic. Alcohol-related consequences that arise from this pattern include physical symptoms, greater consumption than planned, embarrassing behaviors,

among other problems. However, multiple reasons lead to the increase of alcohol consumption in Argentinean young adults, especially motives associated with social factors. The aim of this study was to examine, in a probabilistic sample of Argentinean young adults (18 – 29 years old), alcohol consumption occurrence and frequency and to identify drinking motives and alcohol-related consequences. A probability sample of 1596 young adults (49,4% women; *M* age = 23,6, *SD* = 3,46) from Argentinean urban areas participated in the study and answered to the Argentinean Social Debt Survey in the third quarter of 2019. We found that 7 out of 10 young adults reported alcohol consumption, among whom 20% reported having experienced negative alcohol-related consequences at least once in the previous year. The main reasons that lead to alcohol use referred to social motives. Specifically, young adults informed that they are used to drink alcohol because it is expected at social gatherings and since all their friends consume alcohol. These results raise awareness about alcohol use patterns and related consequences and contribute to the development of interventions aimed to reduce its consumption, considering social factors and drinking motives.

Keywords: Argentinean Social Debt Survey, alcohol use, young adults, motives

Involvement of 5-HT_{2A} and 5-HT_{2C} receptors in the reinforcing effects of ethanol in male mice

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ABSTRACT

Alcohol (ethanol) use disorder (AUD) is associated with marked social, physiological, and psychological consequences to the user. Studies suggest that serotonin (5-hydroxytryptamine, 5-HT) plays a major role in alcohol abuse. Several receptor subtypes modulate the role of 5-HT in AUD, but evidence indicates that 5-HT_{2A} and 5-HT_{2C} receptors may be directly involved in the reinforcing effects of alcohol due to their brain localization and interaction with the mesolimbic dopaminergic system. The objective of the present study was to evaluate the role of serotonin 5HT_{2A} and 5HT_{2C} receptors in the reinforcing effects of ethanol using the two-bottle choice procedure in male mice. Male mice had intermittent 15-hour access to ethanol (10% v/v) in a two-bottle choice procedure for 30 days, with the following treatments being administered before self-administration sessions: vehicle, the 5-HT_{2A} receptor antagonist M100907 (M100, 1 mg/kg) or the 5-HT_{2C} receptor antagonist SB-242084 (SB, 1 mg/kg). After a drug-free period, animals were submitted to re-exposure tests under the same conditions as during acquisition, but without pretreatments before re-exposure sessions. Our preliminary findings show that while treatment with M100 and SB did not significantly affect ethanol intake and preference during acquisition, treatment with both antagonists decreased ethanol preference and intake during re-exposure tests. These findings suggest that both 5-HT_{2A} and 5-HT_{2C} receptors are involved in the reinforcing effects of alcohol in the two-bottle choice paradigm.

Keywords: Ethanol, 5-HT_{2A}, 5HT_{2C}, mice, two-bottle choice

The administration of Alda-1 reduces both ethanol and nicotine chronic intake

in a rat model of concurrent consumption of alcohol and nicotine

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ABSTRACT

Alcohol and nicotine are the most commonly used substances of abuse. Use disorders involving these substances often take place together increasing the probability of a worse clinical outcome than individuals who only abuse one of these drugs. In addition, available pharmacotherapy for the treatment of alcohol and nicotine disorders has shown to be ineffective in the management of the co-abuse of these substances. Recent studies in our lab have shown that the administration of Alda-1, a pharmacological activator of ALDH2, can reduce chronic ethanol intake and also chronic nicotine intake in rats. This work is aimed at determining the effect of the administration of Alda-1 in a rat model of chronic concurrent consumption of alcohol and nicotine. Two groups of alcohol-preferring UChB rats (n=14/group) were exposed to a three-bottle free choice paradigm, where they could choose whether to drink water, 30% ethanol, or 100 mg/L nicotine solutions during approximately 20 days, reaching a mean consumption of 17,2 g/kg of ethanol and 3,9 mg/kg of nicotine. Then, rats were administered with Alda-1 (25 mg/kg, i.g.) or vehicle for 7 days to evaluate the effect on chronic concurrent alcohol and nicotine consumption. Results showed that Alda-1 administration reduced by 75% both ethanol and nicotine consumption compared to rats treated with vehicle. The effect of Alda-1 was reversible since animals recovered their basal alcohol and nicotine

consumption upon discontinuation of the treatment. These findings suggest that Alda-1 could be a potential pharmacotherapy for alcohol and nicotine co-abuse.

Keywords: co-abuse, alcohol, nicotine, Alda-1, UChB rats

HCN2 inhibition in alcohol preferring rats to avoid dopamine peak in nucleus accumbens

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ABSTRACT

Mesocorticolimbic system is a primal neuronal pathway involved in reinforcement of survival natural rewards as food consumption or sexual activity, this system is conformed for dopaminergic neurons that project their axons from ventral tegmental area (VTA) to nucleus accumbens (NAc) and other structures. Ethanol and other abuse drug and have the capacity to activate the dopaminergic activity of mesocorticolimbic system, what translate into an increase of release of dopamine in NAc. HCN2 ion channels (Hyperpolarization-activated cyclic nucleotide-gated) are responsible of pacemaker activity of dopaminergic neurons in sinoatrial node and VTA; this channel has four isoforms (HCN1-4), HCN2 is the most abundant isoform in VTA. Recent studies of our laboratory suggest that HCN2 ion channels are involved in alcohol consumption, in these studies, HCN2 was sobrexpressed and silenced in VTA of UChB rats, that results in an increase and diminution of alcohol consumption respectively. ZD7288, MEL55A and 4e are pharmacological inhibitors of HCN, each with a different affinity for HCN2, with 4e being the most

selective, but they are never tested in an alcoholism model. In this work we synthesize 4e, and evaluate the dopamine release in NAc, when a dose from HCN inhibitor (ZD7288, MEL55A or 4e) is administrate in cerebral ventricle in UChB rats; the samples of dopamine are obtained with microdialysis in vivo and measured with HPLC coupled to electrochemical detection. The objective is use HCN inhibitors to avoid the dopamine increase when we administrate an intraperitoneal dose of ethanol.

Keywords: alcoholism, dopamine, Nucleus accumbens, microdialysis, HCN ion channels, HCN inhibition, UChB rats

Participation in pregaming and risk profiles among university students in Argentina

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ABSTRACT

Aims: There is abundant literature linking pregaming, a drinking practice highly prevalent among Argentine students, to harmful drinking. The main objective of this study is to expand the current knowledge and evidence about pregaming in Argentina by analyzing the students' decision. In the analysis are considered the preferences of taking risks to health loss due to alcohol and other psychoactive substances use. **Methods:** Primary data of 1321 university students (aged 18-25) from two national universities of the center region (UNC, n=678) and west region (UNCU, n=643) were used. The students completed a confidential survey and did not receive any compensation. The decision to participate in pregaming was analyzed employing a discrete choice model, and risk preferences were identified by using Latent Class Analysis (LCA). **Results:** Four profiles of students are identified: all-in players (46%) are the

ones with the greatest probability of having risky behaviors, early-onset players (36%), later-onset players (15%) and cautious players (3%). Our findings suggest that the preferences toward risk are associated with the decision to participate in pregaming, namely, belonging to all-in players class is associated with a greater pregaming likelihood. Conclusion: Our contribution on harmful drinking behaviors among Argentinian college students, a highly exposed population to alcohol and other psychoactive substances, is relevant for the design and implementation of targeted interventions at educational levels, considering that risk profiles are linked to facts prior to university entrance, as it is the onset age of substance use.

Keywords: Argentinean college students, alcohol use, latent class analysis

MicroRNAs in the brain of mice that voluntarily drink ethanol chronically

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ABSTRACT

The transition from recreational ethanol consumption to an alcohol use disorder involves oxidative stress and neuroinflammation in the brain reward system and hippocampus, altering the reward circuits. The brain responds to oxidative stress and neuroinflammation by the activation of microglia and astrocytes. MicroRNAs can inhibit the translation of hundreds of mRNA. Proinflammatory miRNAs are increased in the brain of animals treated with ethanol chronically. We studied microRNA levels in the brain of C57BL/6 mice that voluntarily drink ethanol every-other-day for 70 days. We analyzed differential expression of miRNAs in tissue homogenates, and

isolated microglia and astrocytes by Fluorescence Activated Cell Sorting. In homogenates, alterations were observed in pro and anti-inflammatory microRNAs of drinking animals compared to controls. Changes in microRNA levels of microglia or astrocytes were of a different subset than in homogenates, suggesting that cell isolation is required to determine local alterations after chronic ethanol consumption.

Keywords: ethanol consumption, microRNA, microglia, astrocytes

Effect of emotion dysregulation on alcohol and marijuana outcomes via internal motives: a longitudinal study

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ABSTRACT

Introduction: Previous studies showed difficulties in emotion regulation is related to self-medicate use of alcohol and marijuana (i.e., substance use to alleviate emotional distress or to increase pleasant emotions). However, longitudinal evidence on these relationships is still scarce. Aim: The present study aimed to longitudinally examine the effect of emotion dysregulation on alcohol and marijuana outcomes (i.e., use and problems) via internal motives (i.e., enhancement and coping) in Argentinian college emerging adults (i.e., aged 18 to 30). Method: A sample of 498 participants completed two online surveys (six months between each) assessing last-month alcohol use and negative consequences, last-three-month marijuana use and associated problems, internal motives (i.e., coping and enhancement) to use alcohol or marijuana and difficulties in negative emotion regulation. Of these participants, 468 (72% women; $M_{age} = 23.62$ $SD = 3.04$) reported last-month

alcohol use, while 241 (63% women; $M_{age} = 23.78$ $SD = 2.92$) reported last-three-month marijuana use. Results: Coping motives mediated the associations of emotion dysregulation with typical week quantity of alcohol use and with negative consequences. Instead, the relationship between emotion dysregulation and marijuana frequency use was mediated by enhancement motives. Discussion: Findings support and extend previous cross-sectional evidence showing that, in students with problems to regulate emotions, motivation to cope with negative affect and to intensify pleasurable sensations could contribute to problematic use of alcohol and marijuana use, respectively. They also provide the basis for developing research that determines whether interventions focused on managing the negative emotional experience are useful in preventing increasing in alcohol and marijuana consumption.

Keywords: alcohol, marijuana, internal motives, emotion dysregulation, longitudinal

Psychological distress and cognitive distortions predict alcohol and marihuana use in Uruguayan citizens

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ABSTRACT

There is an increasing interest in finding factors that predict substance use in the adult population, as the use of these substances is associated with significant negative effects. Among other factors, psychological distress has been associated with substance use. This distress may act via a series of cognitive distortions, such as polarized thinking, overgeneralization, and personalization. The effects of distress, in turn, could be counteracted by

emotional regulation strategies. This study analyzed the predictive value of these variables upon alcohol or marihuana use. A sample of 1132 Uruguayan citizens answered an online survey compiling the Kessler K-10 inventory, the inventory of automatic thoughts (Ruiz y Luján, 1991), the emotion regulation questionnaire (ERQ) and several ad-hoc questions on alcohol and marihuana use. Hierarchical regression analyses, one for each substance, indicated that men were more likely to use either substance than women, and a younger age was associated with greater endorsement of marihuana use. Likewise, those participants with greater scores of psychological distress were more likely to use either substance. Interestingly, the addition of cognitive distortions significantly enhanced the predictive power of the model predicting marihuana use. Those exhibiting greater mind reading and catastrophic vision, yet lower personalization and fallacy of justice, endorsed greater marihuana use. Psychological distress was no longer predictive of marihuana use after adding these variables, suggesting that its effect was mediated by these cognitive distortions. These results pinpoint potential avenues for intervention to reduce marihuana and alcohol use.

Keywords: alcohol, psychological distress, cognitive distortions, emotion dysregulation

Folate administration at pregnancy ameliorates the facilitatory effects of prenatal ethanol exposure on postnatal ethanol intake

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ABSTRACT

Introduction: Prenatal ethanol exposure (PEE) is associated with numerous behavioral deficits and greater likelihood of ethanol intake at adolescence. The prenatal administration of folate is a promising approach to reduce the effects of PEE, albeit its impact is still under analysis. Objectives: We tested, in male and female Wistar rats, if prenatal folate administration modulated the effects of PEE on ethanol intake and preference. Methods: This experiment involved 119 adolescent Wistar rats derived from dams given folate (20 mg/kg, gestational days –GD- 13-20) + ethanol (2.0 g/kg, GD 17-20), ethanol or only vehicle at pregnancy. The offspring of these rats was tested for ethanol intake and percent preference vs. water, via two-bottle intake tests (length: 24 h), conducted on postnatal days (PDs) 28, 30, 35 and 36. Results: PEE significantly enhanced absolute and percent ethanol intake, when compared to the control group (i.e., rats given only vehicle). The rats given folate before PEE did not differ from controls. These effects suggest that folate inhibits the facilitatory effect of PEE upon (absolute and percent) ethanol intake at adolescence.

Keywords: folate, rat, prenatal ethanol exposure, alcohol, protective effects

Illustration of a Novel Gut-Brain Axis of Alcohol Withdrawal, Withdrawal-Associated Depression, Craving in Patients with Alcohol Use Disorder

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ABSTRACT

Alcohol use disorder (AUD) patients exhibit domains such as alcohol withdrawal, depression, and craving. The gut-immune response may play a significant role in expressing these AUD domains. This study examined the role of intestinal permeability, pro-inflammatory cytokines, and hormones levels on the AUD domains. Forty-eight AUD patients [male (n=34) and female (n=14)] aged 23-63 yrs. were grouped categorically using the Clinical Institute Withdrawal Assessment of Alcohol Scale (CIWA) as clinically significant (CS-CIWA [score>10] Gr.1 [n=22]), and clinically not-significant group (NCS-CIWA [score≤10] Gr.2 [n=26]). Clinical data (CIWA, 90-day timeline followback [TLFB90], and lifetime drinking history [LTDH]) and blood samples (for testing pro-inflammatory cytokines, and hormones, and markers of intestinal permeability) were analyzed. A sub-set of 13 AUD patient were assessed for craving response towards drug-seeking using Penn-Alcohol Craving

Score (PACS). Gr.1 patients exhibited unique, higher, and significant effects of association on the withdrawal domain (LPS, adiponectin, IL-6, and IL-8); and withdrawal-associated depression domain (LPS, sCD14, IL-6, and IL-8). Craving (assessed by PACS, Penn-Alcohol Craving Scale) could be described by the gut-dysregulation (LBP and Leptin) and candidate proinflammatory (IL-1 β and TNF- α) markers. Such pathway model describes the heavy drinking phenotype, HDD90 with even higher effects ($R^2=0.955$, $p=0.006$) in the AUD patients who had higher ratings for craving (PACS>5). Interaction of gut-dysfunction, cytokines involved in both inflammation and mediating-chemotactic activity constitutes a novel pathophysiological gut-brain axis for withdrawal, and withdrawal-associated depression and craving domains in AUD. AUD patient with higher craving show higher reinforcing effects of the gut-brain axis response for heavy drinking.

Keywords: AUD, Craving, Cytokines, Depression, Gut-Brain Axis, Withdrawal

Ethanol exposure during the third trimester-equivalent of development affects GPx1 and scaffolding GIT1 protein expressions in liver

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ABSTRACT

Ethanol (EtOH) exposure throughout gestation and breastfeeding periods leads to multiples adverse outcomes in the hepatic system. Under oxidative stress, alterations in liver are related to the inhibition of induced nitric oxide synthase activity in sinusoidal

cells as a consequence of the G-protein-coupled receptor (GPCR)-kinase interacting (GIT1) low expression. Here, we hypothesized that both glutathione peroxidase 1 (GPx1) and GIT1 could be altered by EtOH exposure during the third trimester human equivalent development. Therefore, we exposed rats during the third trimester-equivalent [postnatal days (PD) 2-8] to moderate levels of maternal EtOH (20%). GPx1 and GIT1 expressions were detected by western blotting, antioxidant activity of GPx and concentration of hepatic carbonyl groups (PC) were determined by spectrophotometry. Serum biochemistry parameter, such as alanine aminotransferase (ALT), glucose (gluc), cholesterol (chol), and triglycerides (TG) were also measured. We found that ethanol decreases both GIT1 and GPx1 expression, affecting the GPx antioxidant activity and conversely increasing the protein oxidation. These results demonstrate, for the first time that the GPx antioxidant system altered by EtOH exposure during the third trimester of development is correlated to a parallel decreased expression of the GIT1 protein.

Keywords: GPx1-antioxidant; GIT1; Ethanol-exposed offspring

Coping motives for drinking as a mediator between anxiety and depression, and alcohol outcomes in community Spanish young adults

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ABSTRACT

Consistent with the medication hypothesis, drinking to cope with negative affect appears to mediate the relationship between mental health and alcohol-related problems, which has been shown in college students. However, there is a lack of evidence in non-university samples that limits the generalization of results. The present study examines the mediating role of coping motives in the relationship between depression and anxiety and alcohol outcomes (frequency and quantity of alcohol use, binge drinking, and alcohol-related consequences). Prospective design with a baseline assessment and a 2-month follow-up. We recruited 334 young adults in the community (mean = 21.1; SD = 2.21) who completed a questionnaire to measure coping motives for drinking and depression and anxiety (Brief Symptom Inventory) at baseline. Eight mediation models were tested, one for each alcohol outcome (at follow-up) for depression and another four for anxiety. The coping motives for drinking mediated the positive relationships between depression and alcohol outcomes, such that higher levels of depression were associated with higher coping motives, which in turn, were associated with higher alcohol-related outcomes. The same results were found for anxiety, except for the relationship between anxiety and binge drinking, which was not mediated by coping motives. Our findings are consistent with the medication hypothesis that "drinking to cope with negative affect" is a critical mediator of associations between mental health and alcohol-related problems in young adults in the community. Training in healthy coping strategies against negative affect should be useful for interventions aimed at reducing alcohol use and their harms.

Keywords: coping motives, alcohol, depression, anxiety, alcohol outcomes; binge drinking

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Relationship between alcohol use and mental health

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ABSTRACT

Clinicians working with alcohol use disorders patients sometimes face a difficult task assessing their patient's psychiatric complaints because heavy drinking associated with alcoholism can coexist with, contribute to, or result from several different psychiatric syndromes. The patient's gender, family history, and course of illness over time also should be considered to attain an accurate diagnosis. The aim of this study is to find out if there is any relationship between AUD and any psychiatric diagnoses. If there is a relationship, which is the most prevalent psychiatric diagnoses? This is a retrospective study, that was performed in two clinics responsible for the treatment of AUD in UHC" Mother Teresa" during January 2018-june 2019. The diagnosis was made based on clinical history of the patients and laboratory as well as imaging findings. In this study were enrolled 330 patients. In this study were enrolled 330 patients. 98 % of them were male. 107 patients had a dual diagnosis in the moment of hospitalization. Patients without a concomitant diagnose consumed 344.8 (\pm 103.1) ml/day alcohol, whereas patients with a concomitant diagnose consumed 404.1 (\pm 123.5) ml/day alcohol with a significant statistically difference between them ($t = 4.7$ $p < 0.01$). Patients that consumed > 350 ml/day alcohol had 1.7 more risk to develop a dual diagnose than those that consumed < 350 ml/day alcohol. Relative risk RR=1.7 95%CI (1.1 – 2.8) $p=0.02$. 45.5% of patients had anxiety

disorder, 15.2% had personality disorder. Anxiety disorder is the most common psychiatric comorbidity at patients with alcohol use disorder. More studies are needed to find out if high doses of alcohol use are associated with dual diagnosis. Till now, the relationship between the amount of alcohol use and the superposition of a psychiatric diagnose remains still unclear.

Keywords: alcohol, dual diagnose, anxiety disorder, personality disorder

Perceived vulnerability and intention of use protective behavioral strategies among Spanish young adults: the mediating role of drinking motives

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ABSTRACT

Perceived vulnerability to alcohol consequences, a central factor in Protection Motivation Theory can motivate people to adopt health-protective behavior. However, systematic review showed that perceived vulnerability is a poor predictor of intention and behavior. From a motivational perspective on alcohol use, perceived vulnerability can be affected by reasons people have drinking. For example, previous studies showed that drinking motives predict perceived vulnerability, and drinking motives are associated high protective behavioral strategies (PBS) use. Thus, drinking motives would explain the relationship between perceived vulnerability and

intention to use PBS. The present study examines if drinking motives (social, enhancement, coping, and conformity) mediate the relationship between perceived vulnerability and intention to use PBS. Prospective design with a baseline assessment and a 2-month follow-up. We recruited 328 young adults (age: $M = 21.15$; $SD = 2.23$) who completed questionnaires to measure perceived vulnerability to negative consequences when consuming alcohol, and when getting drunk and drinking motives at baseline, and intention to use PBS at follow-up. Mediation analyses showed that higher perceived vulnerability was related higher positive motives (social and enhancement), which was related lower intention PBS use. Negative motives for drinking (coping and conformity) not mediated this relationship. Our findings support the usefulness of correcting self-perceptions risk of alcohol use in interventions aimed at reducing alcohol-related harm in young adults, and drinking positive motives should be included as a component of these interventions.

Keywords: perceived vulnerability, alcohol, drinking motives, intention, protective behavioral strategies

Role of 5-HT2A receptors in the development of ethanol-induced conditioned place preference in male mice

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ABSTRACT

Studies suggest that serotonin receptors may play a significant role in the abuse-related behavioral effects of ethanol, with a potential role for 5-HT2A receptors. However, whether 5-HT2A receptors are involved in the rewarding effects of ethanol remained unknown. This work aimed to investigate the role of 5-HT2A

receptors in the development of conditioned place preference (CPP) induced by ethanol (Eth) in mice. Forty adult male Swiss mice were used in this study. The CPP protocol consisted of habituation to the apparatus (2 days), a drug-free pre-conditioning test, an 8-day conditioning period and a drug-free post-conditioning test. During conditioning sessions, on even days animals received an i.p. injection of saline, vehicle or the 5-HT_{2A} receptor antagonist M100907 (M100) at the doses of 0.1, 0.3 or 1 mg/kg, followed by an i.g. injection of saline or Eth (2 g/kg) and were placed in one side of the apparatus. On odd days, all animals received a saline injection and were placed in the opposite side of the apparatus. The results show that animals treated with vehicle showed a preference for the Eth-paired compartment during the post-conditioning test. On the other hand, animals treated with 0.3 and 1.0 mg/kg M100 showed a significant decrease in CPP score compared to animals treated with vehicle. Our findings show that the 5-HT_{2A} antagonist dose-dependently blocked the development of Eth-induced CPP in male mice, suggesting a role for 5-HT_{2A} receptors in the rewarding effects of Eth.

Keywords: alcohol, serotonin, conditioned place preference, mice.

Effects of physical exercise on long-lasting behavioral consequences of social isolation and ethanol intoxication during adolescence

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ABSTRACT

Social isolation and ethanol consumption may influence brain development in adolescence and may cause long-lasting behavioral consequences. Thus, the present study aimed to assess whether social isolation and ethanol consumption during adolescence could cause memory impairment and changes in anxiety - and depression-like behaviors in adulthood. Further, if physical exercise could revert such deficits. Male Swiss mice were allocated into eight experimental groups: isolated-ethanol-sedentary (ESi) (n=6), isolated-ethanol-exercise (EEi) (n=7), isolated-water-sedentary (ASi) (n=6), isolated-water-exercise (AEi) (n=8), grouped-ethanol-sedentary (ESa) (n=8), grouped-ethanol-exercise (EEa) (n=8), grouped-water-sedentary (AAs) (n=7), grouped-water-exercise (AEa) (n=8). Animals from "ethanol" groups underwent the intermittent ethanol access and ethanol vapor chamber protocol, and from the "exercise" group underwent the forced physical exercise protocol (treadmill) for 4 weeks. It was observed an increase in ethanol consumption (from the third week) by isolated groups (7.8 ± 1.7 g/kg) compared to grouped animals (6.4 ± 1 g/kg) ($p < 0.05$). Moreover, the animals in the EEi group showed a decrease in the time spent in the open arms ($p = 0.0563$), as well as in the number of unprotected heads dipping ($p = 0.0091$) when compared to the other groups ($p = 0.0091$). Regarding the memory test, it was observed that the animals from the EEi group did not recognize the new object, in the tests performed 1 and 24 hours after the training, presenting short- and long-term memory impairments. For the depressive-type behavior, the ESi group showed an increase in the immobility time when compared to the other groups ($p < 0.05$). Social isolation, during adolescence, leads to long-lasting neurobiological plasticity, and increases alcohol consumption.

Keywords: social isolation, alcohol, memory, mice

Evidence of the participation of the muscarinic system and the therapeutic potential of biperiden in ethanol use disorders

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ABSTRACT

Studies suggest that muscarinic cholinergic receptors have an important role in dopamine release in the mesolimbic system. Furthermore, studies show that they can modulate the drug's reinforcement and drug craving. First, we evaluated the effect of systemic biperiden administration, a muscarinic cholinergic (M1) antagonist receptor, on alcohol-conditioned place preference (CPP), and dopamine, HVA, and DOPAC levels in the nucleus accumbens. Second, we examine changes in M1 muscarinic gene expression, through rt-PCR, in late abstinence (21 days) after prolonged exposure to the alcohol vapor chamber. Our results demonstrated that the biperiden administration at different doses (1, 5, and 10 mg/kg i.p.) blocked the expression of the CPP induced by ethanol ($F(3, 34) = 11,24, p < 0,05$). Moreover, we observed that Biperiden reduced dopamine ratio (HVA + DOPAC / DA) in the nucleus accumbens ($[F(3, 27) = 5,43, p < 0,05]$). Finally, we observed that chronic exposure to the alcohol vapor chamber caused an increase in the expression of the M1 receptor gene [$F(2, 18) = 6,826; p < 0,05$] in the late abstinence. Our data suggest biperiden may be a promising drug for alcohol use disorders. Its action mechanics may involve changes in the dopaminergic and cholinergic neurotransmission in the mesolimbic system.

Keywords: alcohol, muscarinic cholinergic receptors, vapor, biperiden.

Identification of alternative splicing events modified by prenatal ethanol exposure

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ABSTRACT

Prenatal ethanol exposure is associated with neurodevelopmental defects and long-lasting cognitive deficits, grouped as fetal alcohol spectrum disorders (FASD). A hallmark of FASD is memory and learning deficits linked to diminished synaptic plasticity in the hippocampus. The molecular mechanisms underlying FASD are incompletely characterized. Alternative splicing modulation is crucial for neurodevelopment and synaptic plasticity. Previous reports have shown that ethanol exposure alters splicing factor expression patterns and therefore splicing synchronization. In this work, we used available RNA-Seq databases to identify alternative splicing events involved in neurodevelopment and synaptic plasticity affected by ethanol exposure. Remarkably, Gene Ontology analysis revealed that the alternative splicing of genes related to RNA processing and protein synthesis was affected by ethanol exposure, suggesting that the alternative splicing of genes

related to post-transcriptional regulation is modified by ethanol. Using cellular and animal models of FASD, we analyzed the expression patterns of splicing events in genes previously predicted in bioinformatic approach. Together our data indicate that ethanol exposure during neurodevelopment alters splicing regulation suggesting a new mechanism contributing with the etiology of FASD.

Keywords: alcohol, FASD, learning, memory

Anxiogenic effect of environmental enrichment in mice submitted to chronic unpredictable stress

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ABSTRACT

Environmental enrichment (EE) is a paradigm that provides rodents several stimuli and works as a protective factor. In this work, we applied EE with the proposal to minimize anxiety-related behaviors induced by chronic unpredictable stress (CUS). Brain regions such as the prefrontal cortex (PFC) and the hippocampus are essential in the stress response due to their neuromodulation on the hypothalamic-pituitary-adrenal (HPA) axis. To investigate the protective role of EE on the modulation of anxiety-like behaviors of mice exposed to CUS. Male Swiss mice were divided into two groups: non-enriched (NE) and EE for 21 days. After 21 days, mice were further subdivided into 4 groups: (1) NENS: NE-non stressed; (2) NEST: NE-stressed; (3) EENS: EE-non-stressed; (4) EEST: EE-stressed. The CUS protocol lasted 11 days and included several stressors. On PND82, animals were submitted to the elevated plus-maze (EPM) test to evaluate anxious-like behaviors.

In the sequence, all mice were euthanized and the blood was collected to measure corticosterone (CORT) levels in plasma. Then, the expression of glucocorticoid receptors (GR) in the hippocampus and PFC regions was evaluated. (n=8-12/group). All procedures were approved by the Animal Use Ethics Commission (CEUA) of the University of São Paulo (nº 1186020719). EE, when associated with CUS, reduced the time spent in the open arms indicating a possible anxiogenic effect, revealed by the EPM. Also, EE animals submitted to CUS presented higher CORT when compared to EE animals submitted to an acute stress. As for the expression of GR, EE reduced the expression of hippocampal GR and increased in PFC. We demonstrated that mice in EE exhibited an anxious phenotype when exposed to CUS. Also, the increase of CORT levels and the changes in GR expression after CUS points to a neuroplastic adaptation of the HPA axis.

Keywords: alcohol, environmental enrichment, stress, mice

Alda-1 administration reduces alcohol relapse and normalize NAc glutamate levels in rats exposed to chronic drinking and forced-abstinence

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ABSTRACT

Chronic ethanol consumption results in elevated extracellular glutamate levels in NAc and an increase of the toxic aldehyde 4-hydroxynonenal (4-HNE), factors that have been associated to alcohol relapse. Recent studies in rats have shown that the administration of Alda-1, an activator of the mitochondrial aldehyde dehydrogenase (ALDH2),

reduces chronic ethanol intake. However, is unknown whether ALDA-1 could reduce alcohol relapse intake or affect glutamate and 4-HNE levels during abstinence. The aim of this work was to determine the effect of Alda-1 in extracellular glutamate, glial glutamate transporter (GLT1), and 4-HNE levels in the NAc of rats exposed to chronic ethanol consumption followed by a forced abstinence period of two weeks. We also determined the magnitude of alcohol relapse upon re-access to ethanol solution. Results showed that chronic ethanol consumption followed by forced abstinence increase NAc glutamate levels by 200%, while animals treated with Alda-1 showed basal glutamate levels similar to control (naïve) rats. No effects of Alda1 were observed on GLT-1 and 4-HNE levels compared to vehicle-treated rats. Importantly, animals treated with Alda-1 reduced by 90% their relapse-like alcohol consumption upon re-access to ethanol solution. These results suggest that Alda-1 could reduce alcohol drinking relapse by decreasing accumbal glutamate levels through a GLT-1-independent mechanism.

Keywords: ethanol, ALDA-1, glutamate, GLT1, 4-HNE.

Alda-1 administration reduces relapse-like ethanol and nicotine consumption in rats: assessment of neuroinflammation and oxidative stress

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ABSTRACT

The administration of Alda-1, a pharmacological activator of ALDH2, has been shown to decrease chronic ethanol or nicotine consumption in ethanol-preferring UChB rats. This study is aimed at determining whether Alda-1 administration reduces relapse-like ethanol or nicotine consumption and its effects on neuroinflammation and oxidative stress markers. Two groups of UChB rats were exposed to chronic ethanol or nicotine use for 90 days, next deprived for 14 days, and re-exposed to the substances for 7 days to set up relapse-like consumption, administering Alda-1 or vehicle during 14 last days of schedule. Neuroinflammation (glial reactivity) and hippocampal oxidative stress markers (GSSG/GSH ratio) were assessed. Alda-1 administration reduced relapse-like ethanol consumption by 92.2% compared to vehicle group and showed a tendency to decrease thickness of primary processes and microglial density in the hippocampus after re-access to ethanol. Ethanol relapse was also associated with a reduction of astrocyte density in NAc, an effect that was less pronounced in animals treated with Alda-1. No significant differences were observed in hippocampal GSSG/GSH ratio between ethanol-consuming groups. Alda-1 administration reduced relapse-like nicotine consumption by 82.3% compared to vehicle group which was associated with an unexpected reduction in hippocampal GSSG/GSH. No differences were observed between vehicle and Alda-1. Alda-1 significantly decreased relapse-like ethanol or nicotine consumption in UChB rats, tended to decrease thickness of primary processes and microglial density, and increased astrocyte density in NAc core in relapse-like ethanol consumption group. The effects of Alda-1 on neuroinflammation markers in the relapse nicotine consumption model are under study.

Keywords: alcoholism, ethanol, nicotine, neuroinflammation, oxidative stress, rats

Episodic Binge-like ethanol reduces skeletal muscle strength associated to atrophy, fibrosis and inflammation in young rats

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ABSTRACT

The consequences of chronic ethanol abuse include alcoholic myopathy, a condition characterized by muscle weakness and atrophy. However, the short- and long-term effects of episodic Binge drinking (BD) on skeletal muscle have been poorly explored. This become relevant because, although BD occurs across all populations, young and sports-related people are especially vulnerable, and there is a low-risk perception about the BD-consequences on skeletal muscle function and athletic performance. We studied the effects of a binge-like ethanol protocol (BEP) on rat skeletal muscle function. Young rats (25days-old) were submitted to episodic BEP (alcohol dose 3g/kg IP, 4 episodes of 2-days ON – 2-days OFF paradigm) or control (saline) (N=6 per group). 2-weeks after last episode, we evaluated skeletal muscle contractile properties and analyzed muscle samples for cellular and molecular pathological markers. Rats exposed to binge-like ethanol present

decreased muscle strength and increased fatigability compared with control animals. We observed that skeletal muscle from rats exposed to BEP present sings of muscle atrophy, evidenced by reduced fiber size and increased expression of atrophic genes. Also, we observed that BEP induces fibrotic and inflammation markers, accompanied by mis-localization of nNOS μ and high levels of protein nitration. Our findings suggest that binge-like alcohol exposure alters contractile capacity and increases fatigue by mechanisms involving atrophy, fibrosis, and inflammation, which remain for at least 2 weeks after alcohol clearance. These pathological features are common to alcoholic myopathy or other neuromuscular diseases and might affect muscle performance and health in the long term.

Keywords: Binge-drinking, Alcoholic Myopathy, skeletal muscle, muscle fatigue, fibrosis, atrophy, inflammation.

Maternal separation stress: consequences on ethanol intake, neuronal activation and the brain endocannabinoid system in adolescent mice

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ABSTRACT

Maternal separation (MS) is an animal model of early-life stress that may lead to increased ethanol intake. MS can promote neuroadaptations associated with addiction-related behaviors in the endocannabinoid system. We evaluated MS impacts on ethanol intake

and neuronal activation levels in brain areas related to reward pathways in adolescent mice. Also, we analyzed MS and ethanol intake effects on the expression of genes encoding for CB1 receptors (CNR1) and endocannabinoid-metabolizing enzymes (MGLL and FAAH) in the dorsal striatum. From postnatal day (PND) 1 to 14, male and female C57BL/6J mice were separated from the dams daily for three hours or left undisturbed (controls) and subjected to behavioral tests from PND 28. In Experiment 1, mice were evaluated in an involuntary ethanol intake protocol followed by operant ethanol self-administration. Immunohistochemistry for Fos was performed in the prefrontal cortex, dorsal striatum, globus pallidus, and substantia nigra. In Experiment 2, mice were exposed or not to a two-bottle choice protocol of ethanol intake, and CNR1, MGLL, and FAAH gene expression in the dorsal striatum were analyzed. Experiment 1 data show that MS increased involuntary ethanol consumption but did not affect operant behavior reinforced by this drug nor Fos expression in all analyzed brain areas. Experiment 2 showed that MS did not impact voluntary ethanol intake but increased preference for ethanol. Also, MS reduced striatal MGLL, despite not altering CNR1 or FAAH expression. Thus, our data suggest that MS augmented involuntary ethanol intake and preference for ethanol solution and reduced striatal MGLL expression levels.

Keywords: stress, alcohol, Fos, endocannabinoid, CB1 receptor, FAAH enzyme, MAGL enzyme

Effect of administration of polyherbal X on rat brain histopathology, malondialdehyd (MDA) levels, and superoxide dismutase activity (SOD) induced with trimethyltin chloride in rats model ischemic stroke

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ABSTRACT

Trimethyltin chloride (TMT) is a neurotoxic compound that causes cell death in human and animal brains. This study aimed to determine the neuroprotective effect of polyherbal extracts consisting of Moringa leaf (*Moringa oleifera* L), meniran (*Phyllanthus niruri* L), and black cumin (*Nigella sativa* L) against pyramidal cells in the hippocampus of rats, increased levels of malondialdehyde (MDA) and superoxide dismutase activity (Trimethyltin chloride-induced SOD in a rat model of ischemic stroke. This experimental study used male Wistar rats which were divided into 7 groups, namely the normal control group, positive control group, negative control group, and 4 groups of polyherbal dose level X (50; 100; 200; 400 mg/kg BW). MDA levels were measured using the Thiobarbituric Acid Reactivity Test (TBARs) method. Measurement of SOD activity was carried out using the Misra and Fridovich method. There was a decrease in the percentage of pyramidal cell damage in the hippocampus at P1, P2, and P3, and the average results of the measurement of MDA levels in the rat brain in 7 groups were 1.9969 nmol/mL, 7.1825 nmol/mL, 1.6076 nmol/mL, 5.1859 nmol/mL, 3.6271 nmol/mL, 2.2537 nmol/mL, 1.6807 nmol/mL. The average results of the measurement of brain SOD activity of rats in 7 groups in a row were 181.21 U/mL, 111.41 U/mL, 181.52 U/mL, 125.76 U/mL, 164.04 U/ mL, 184.44 U/mL, 190.33 U/mL. The results obtained conclude that the administration of polyherbal X at a dose of 400 mg/kg BW will decrease

pyramidal cell damage in the hippocampus and provide an antioxidant effect by reducing MDA levels and increasing SOD activity.

Keywords: Moringa leaf (*Moringa oleifera* L), meniran (*Phyllanthus niruri* L), black cumin (*Nigella sativa* L), brain histopathology, trimethyltin chloride

Ethanol exposure during the third trimester-equivalent of development affects GPx1 and scaffolding GIT1 protein expressions in liver

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ABSTRACT

Ethanol (EtOH) exposure throughout gestation and breastfeeding periods leads to multiples adverse outcomes in the hepatic system. Under oxidative stress, alterations in liver are related to the inhibition of induced nitric oxide synthase activity in sinusoidal cells as a consequence of the G-protein-coupled receptor (GPCR)-kinase interacting (GIT1) low expression. Here, we hypothesized that both glutathione peroxidase 1 (GPx1) and GIT1 could be altered by EtOH exposure during the third trimester human equivalent development. Therefore, we exposed rats during the third trimester-equivalent [postnatal days (PD) 2-8] to moderate levels of maternal EtOH (20%). GPx1 and GIT1 expressions were detected by western blotting, antioxidant activity of GPx and concentration of hepatic carbonyl groups (PC) were determined by spectrophotometry. Serum biochemistry parameter, such as alanine aminotransferase (ALT), glucose (gluc), cholesterol (chol), and triglycerides (TG) were also measured. We found that ethanol decreases both GIT1 and

GPx1 expression, affecting the GPx antioxidant activity and conversely increasing the protein oxidation. These results demonstrate, for the first time that the GPx antioxidant system altered by EtOH exposure during the third trimester of development is correlated to a parallel decreased expression of the GIT1 protein.

Keywords: liver, alcohol, protein expression, gestation

Binge-like ethanol drinking during adolescence increases ethanol consumption at adulthood in Wistar rats

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ABSTRACT

The earlier the onset of alcohol use, the greater the probability of problematic use of alcohol later in life. Several clinical studies, however, suggest that the initial contact with alcohol is not as relevant, as a predictive milestone for subsequent problematic substance use, as the first intoxication or drunkenness episode. This suggests that pre-clinical models of “early alcohol initiation” should focus on a type of drug exposure akin to that of drunkenness. The present study assessed the effects of adolescent binge-like ethanol intake, on ethanol self-administration at adulthood. We exposed Wistar rats, males or females, to self-administered 8-10% (v/v) ethanol during 2 hours, three times a week during postnatal days (PDs) 31-50. Shortly after the rats were tested for total distance traveled in the Open Field (OF, PD 52) and recognition memory (PD 54); and then at adulthood tested for free-choice drinking during PDs 87-97 in intermittent two-bottle intake tests. Results show that adolescent binge drinking decreased distance traveled in the OF while did not affect recognition memory. The rats that had been

initially exposed to ethanol at adolescence drank, during the intake tests conducted at adulthood, significantly more than those that had their first experience with ethanol at adulthood. Adult ethanol intake was greater in females than in males. The study indicates that binge ethanol drinking is associated with heightened ethanol intake at adulthood. Preventing or delaying the use of alcohol to adolescents should reduce the likelihood of problematic alcohol use or alcohol-related consequences.

Keywords: ethanol intake, binge drinking, adolescence