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ANALES DE LA FACULTAD DE MEDICINA

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X Meeting Santiago-Chile
October 28–29, 2024

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AUTHOR INDEX, POSTER ABSTRACT

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La Sociedad Latinoamericana para la Investigación Biomédica en Alcoholismo (LASBRA) es una organización científica dedicada a promover la investigación, el intercambio de conocimientos y la formación de nuevas generaciones de científicos enfocados en el estudio de los trastornos por uso de alcohol y sus consecuencias. Como parte de su misión de integrar a la comunidad científica regional e internacional, los días 28 y 29 de octubre de 2024, LASBRA celebró su X Reunión Científica. El evento tuvo como sede la Facultad de Ciencias Químicas y Farmacéuticas de la Universidad de Chile, en Santiago.

El encuentro congregó a 61 asistentes, entre ellos destacados investigadores y 40 estudiantes de pregrado y posgrado provenientes de Argentina, Brasil, Chile, España, Estados Unidos y Uruguay. A través de conferencias magistrales, simposios y la presentación de 35 pósteres científicos, se abordaron temáticas de vanguardia, tales como terapias con células madre, nuevos blancos moleculares, modelos preclínicos y los efectos de la exposición prenatal al etanol.

Con el objetivo de fortalecer el futuro de la investigación en la región, el evento contó con el apoyo de la International Society of Neurochemistry (ISN) para otorgar 20 becas de asistencia a estudiantes y fue auspiciado por el Proyecto Anillo ANID-Chile (ACT210012). Durante la reunión se otorgó el "Premio a la Trayectoria LASBRA 2024" al Prof. Yedy Israel por sus históricos aportes al campo. Asimismo, se oficializó la nueva directiva para el período 2025-2026, asumiendo la presidencia el Prof. Paul Ruiz (Universidad de la República, Uruguay).

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ALDA-1 decreased relapse to ethanol or nicotine consumption: assessment of neuroinflammation and brain oxidative stress

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New pharmacological strategies are needed to treat alcohol and tobacco abuse due to the low effectiveness of currently available treatments. Studies in our lab have demonstrated that ALDA-1, a pharmacological activator of the ALHD2 enzyme, reduced acquisition and chronic ethanol consumption in ethanol-preferring UChB rats. Moreover, these rats voluntarily consume nicotine, representing a tool for the study of new pharmacological therapies for tobacco addiction. Also, both addictions have been associated with the development of neuroinflammation and oxidative imbalance in the brain; it is worthwhile to prioritize research in this area to reduce brain consequences related to alcohol- or tobacco-consuming.

Studies in our lab demonstrated that ALDA-1 administration relapse-like ethanol consumption and reduced chronic and relapse-like nicotine consumption. At least for relapse-like ethanol consumption, this decrease was associated with discrete and specific changes in neuroinflammation observed in HPC and NAc. No significant differences in neuronal relative abundance in HPC were assessed through NeuN determination in HPC. No changes were observed in oxidative stress either, except for the MDA concentration in the HPC of rats that consumed ethanol and treated with ALDA-1, which showed a tendency to decrease in this parameter. Also, the GSSG/GSH ratio showed a decrease in the groups that consumed nicotine.

ALDA-1 administration significantly decreased relapse-like ethanol consumption and chronic and relapse-like nicotine consumption. However, this effect was not related to changes in neuroinflammation and oxidative stress markers.

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Intermittent exposure to a single bottle of ethanol modulates stress sensitivity: impact of age at exposure initiation

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Adolescent binge drinking is often associated with life-long alcohol misuse and may contribute to adverse health outcomes that emerge later in life. Our work has utilized two common models of adolescent binge drinking in rats, including intermittent ethanol gavage (4.0 g/kg ig on a 3-day on, 2 day off schedule for 4 cycles) and exposure to a single bottle of 10% ethanol (2 days on, 2 days off for 12 cycles) across adolescent neurodevelopment. Both procedures produce tell-tale signs of neuroimmune sensitization evidenced by exacerbated induction of neuroimmune genes when adolescent-exposed rats were challenged with lipopolysaccharide (100 µg/kg LPS;) as adults. These effects were most evident in the hippocampus and when ethanol exposure was initiated during early adolescence. Furthermore, recent studies showed that adolescent binge models may also contribute to Blood-Brain Barrier (BBB) dysfunction and vascular remodeling of the cerebral cortex. Importantly, both of these persistent neurovascular changes were observed exclusively in male Sprague Dawley rats, suggesting that females may be protected against ethanol-mediated neurovascular dysfunction. Converging evidence suggests that perivascular microglia may play an important role in both neuroimmune sensitization and neurovascular dysfunction produced by adolescent ethanol exposure. Together, the long-lasting effects of adolescent ethanol exposure may have important implications for later stress reactivity, ethanol reinforcement processes, and the trajectory of overall brain health in aging.

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Zebrafish as a tool for the study of nicotine and ethanol addiction

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Nicotinic acetylcholine receptors (nAChR) are part of the family of ion channels activated by ligands. There are several subtypes of nicotinic receptors, given their pentameric nature, among which the $\alpha_2\beta_2$ and the α_7 subtypes appear to be the most abundant in the Central Nervous System (CNS). They are responsible for the permeability of the cell membrane to sodium and calcium ions, having an essential function in the central nervous system, modulating the release of different neurotransmitters, such as dopamine, and norepinephrine, among others. Nicotinic acetylcholine receptors are associated with mood disorders such as anxiety and abuse of addictive substances such as nicotine addiction and ethanol consumption. Our work has oriented toward the search for molecules of natural or synthetic origin that show affinity for nicotinic receptors, particularly the $\alpha_4\beta_2$ nAChR subtype, acting as an agonist or antagonist ligands. In recent years we have ventured into in vivo models, finding that the zebrafish appears to be a useful tool, given its versatility and amount of experimental animals, for the search of substances with potential pharmacological activity, which allows us to project these selected substances to a rat's model to extend our studies. Currently, we have used the Novel Tank Diving Test (NTT) paradigm as an anxiety or stress model and a Conditioning Place Preference model, similar to the one used in rats, to generate a behavior profile in zebrafish, which allowed us to discover new substances with a potential therapeutic effect against nicotine addiction and ethanol consumption.

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Extracellular vesicles derived from mesenchymal stem cells ameliorate in vivo imaging of mouse neuroinflammation induced by chronic alcohol consumption

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Mesenchymal stem cells (MSC) are anti-inflammatory and immunoregulatory cells, and their EVs are considered as promising molecules for treatment of immune, inflammatory and degenerative diseases. Our previous studies demonstrated that MSC-derived EVs restored the neuroinflammation induced by binge ethanol drinking in adolescence. The aim of this study is to analyze if MSC-derived EVs are capable to reduce the microPET imaging of neuroinflammation induced by chronic alcohol consumption. Adult mice were treated with drinking water containing 10% (v/v) ethanol for 3 months. The EVs were obtained from human adipose tissue-derived MSCs and administered into the tail vein (20 µg/dose) every ten days during ethanol treatment. Our results showed that ethanol treatment increased the 18 F-FDG uptake in the whole-brain 3D images and in the coronal sections of prefrontal cortex, striatum and hippocampus. Interestingly, the administration of MSC-derived EVs was able to reduce the increased binding of the tracer in ethanol-treated mice. In addition, these EVs were also able to ameliorate the upregulation in the expression of proinflammatory genes in prefrontal cortex, striatum and hippocampus, and the cognitive impairments induced by alcohol treatment. These results suggest that MSC-derived EVs could be an efficient treatment to decrease the neuroinflammation and brain damage induced by the chronic alcohol consumption.

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Mesenchymal stem cells and their secretion products as potential therapeutic agents against addiction

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The administration of mesenchymal stem cells (MSCs) has emerged as a promising therapeutic strategy for brain neurodegenerative and inflammatory diseases due to their pleiotropic mechanisms of actions that include cell replacement, promotion of survival via paracrine signaling, modulation of inflammation, and reduction of oxidative damage. MSCs show low immunogenicity, allowing allogeneic transplantation without immunosuppression and have successfully reduced brain oxidative stress and inflammation in animal models of oxidative and inflammatory diseases. MSCs appear as highly attractive candidates for the treatment of addictions. In significant proof-of-concept studies, our research group demonstrated that a single intra-cerebroventricular administration of rat bone marrow-derived or adipose tissue-derived MSCs, or human adipose tissue-derived MSCs to alcohol-preferring UChB rats that had consumed ethanol chronically reduced their ethanol intake by 75% and inhibited alcohol relapse up to 85%. Such an effect was also achieved following the intravenous administration of spheroids derived from human MSCs to UChB rats after chronic ethanol intake. The therapeutic effects of MSCs administration were correlated with a significant reduction of brain oxidative stress and neuroinflammation. These results suggest that MSCs potent antioxidant and anti-inflammatory capabilities modulate ethanol consumption, highlighting their potential as therapeutic agents against addiction.

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Food availability and composition can influence ethanol drinking and anxiety-like behavior in mice

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Environmental factors, such as food availability and composition, play a crucial role in ethanol drinking behaviors. We used a two-bottle choice Intermittent Overnight Drinking (IOD) protocol, where female and male C57Bl/6 or Swiss Webster mice had either access to chow or no food access. Additionally, we examined how isoflavones, a micronutrient not standardized in rodent chow, impact ethanol drinking and anxiety-like behaviors. Mice underwent 12 testing sessions using lickometer devices. During each session, they had access to two bottles (water and 10% ethanol) for 16 hours, starting 2 hours before lights-off. For anxiety tests, we used the light-dark box and elevated plus maze. Food availability increased liquid consumption, but strain and liquid specificity varied: food increased ethanol intake in C57Bl/6 mice but water intake in Swiss Webster mice. Microstructural analysis showed food raised both ethanol licks and bouts in female C57Bl/6 mice, while increasing water licks without altering bout numbers in Swiss mice. Our facility's chow (NUVILAB CR-1) lacked puerarin, an isoflavone linked to reduced anxiety and ethanol consumption. Thus, we supplemented mice with puerarin in their water for one month. Puerarin reduced ethanol consumption and preference, and produced anxiolytic effects in the Light-Dark Box test. These findings underscore the importance of environmental factors, such as diet, in shaping ethanol drinking and anxiety-like behaviors in mice.

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Changes in ethanol-induced effects in a knock-in mouse model with mutations in α_1 and α_2 glycine receptor subunits

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Glycine receptors (GlyRs) are known to be potentiated by physiologically relevant concentrations of ethanol, and mutations in the intracellular loop of the α_1 and α_2 subunits have been shown to reduce this potentiation. Previous studies with knock- in (KI) mice bearing these individual mutations indicated that the α_1 and α_2 subunits play significant roles in ethanol-induced sedation and ethanol consumption. This study aimed to determine whether the combined effect of both mutations in a double knock-in (2xKI) mouse model, created through selective breeding, would further influence cellular and behavioral responses to ethanol. Using electrophysiological recordings we investigated the effects of ethanol on GlyRs and assessed ethanol-induced neuronal activation in the nucleus accumbens (nAc) using c-Fos immunoreactivity and the genetically encoded calcium indicator GCaMP6s. Additionally, we evaluated ethanol-induced behaviors using the open field test, loss of righting reflex (LORR), and the drinking in the dark (DID) paradigm. Our findings revealed that ethanol did not potentiate GlyRs or affect neuronal excitability in the nAc of 2xKI mice. Moreover, ethanol decreased the calcium signal in wild-type (WT) mice, while no change was observed in 2xKI mice. Interestingly, baseline c-Fos levels were elevated in 2xKI mice in the absence of ethanol. In behavioral assays, 2xKI mice recovered more quickly from a sedative dose of ethanol and showed higher ethanol intake on the first day of the DID test compared to WT mice. Furthermore, the open field test indicated that 2xKI mice exhibited reduced anxiety-like behavior relative to WT mice. These results suggest that the α_1 and α_2 subunits of GlyRs are crucial targets for modulating the sedative effects of ethanol and regulating ethanol consumption.

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

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High-ethanol intake induces a neuroinflammatory response, which has been proposed as one of the mechanisms responsible for the maintenance of chronic ethanol consumption. Neuroinflammation increases glutamate levels, that trigger dopamine release at the corticolimbic reward areas driving relapse and 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 had not been studied. We previously reported that the administration of fenofibrate to ethanol drinking UChB rats increased catalase levels in the liver, which accelerates the rate of ethanol oxidation to acetaldehyde. Accordingly, animals showed a marked accumulation of acetaldehyde in the blood, which would lead to aversive effects that decreased ethanol consumption. Now, we studied whether the administration of fenofibrate in the withdrawal stage after chronic ethanol consumption reduces voluntary intake when alcohol is offered again to the animals (relapse-type drinking). Animals treated with fenofibrate decreased alcohol consumption by 80% during post-abstinence relapse. One possibility is that fenofibrate could be normalizing the glutamatergic tone since a reversal of the alcohol-induced decrease in astrocytic glutamate transporter (GLT-1) expression was observed. Furthermore, fenofibrate decreased the expression of the proinflammatory cytokines TNF-α, IL-1 and IL-6, and of an oxidative stress- induced gene (heme oxygenase-1) in the hippocampus, nucleus accumbens, and prefrontal cortex. Fenofibrate also reduced oxidative stress, as well as increased M2-type microglia (with anti- inflammatory properties) and decreased phagocytic microglia in the hippocampus. These findings highlight the potential of fenofibrate, an FDA-approved dyslipidemia medication, as a supplementary approach to alleviating relapse severity in individuals with alcohol use disorder (AUD) during withdrawal.

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Secretome derived from mesenchymal stem cells as a new biodrug for the treatment of drug addictions: toward the identification of therapeutic molecules

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Chronic consumption of addictive drugs leads to neuroinflammation and oxidative stress, which inhibit the astrocyte Na-glutamate-transporter (GLT-1) in the brain reward circuit, proposed to perpetuate drug addiction. The secretome derived from mesenchymal stem cells (MSCs) contains potent anti-inflammatory and antioxidant molecules. We demonstrated that the intranasal administration of the secretome derived human MSCs to rats voluntarily drinking ethanol, nicotine or morphine: (a) inhibited voluntary drug intake and relapse; (b) inhibited drug-induced neuroinflammation and oxidative stress; and (c) increased brain GLT-1 levels. Knockdown of GLT-1, by the administration of an antisense oligonucleotide, fully abolished the inhibitory effect of MSC-derived secretome on drug intake, suggesting that GLT-1 mediates the therapeutic effects of MSCs. Using proteomic analysis and artificial intelligence, we conducted multiple protein-protein interaction analysis in the GLT-1 network (PPI-analysis), which allowed the identification of proteins in the MSC secretome that are strongly represented in the GLT-1-PPIs network. The most promising candidates were recombinantly produced and encapsulated in liposomes for intranasal testing in animal models of drug addiction. Overall, these studies indicate that the administration of MSC-derived secretome or specific molecules contained within it offers translational opportunities for the treatment of drug use disorders.

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Blockade of HCN ion channels as a potential mechanism to reduce the rewarding effects of ethanol

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A recognized target for the addictive effects of ethanol is the dopaminergic circuitry of the ventral tegmental area (VTA). Ethanol can stimulate VTA dopamine neurons by increasing their activity, thus increasing dopamine release in the nucleus accumbens (NAc). The excitability of VTA dopamine neurons is controlled mainly by the depolarizing action of hyperpolarization-activated cyclic nucleotide-gated (HCN) ionic channels. In vitro evidence shows that ethanol can activate HCN channels and that HCN blockers can inhibit these activating actions of ethanol. HCN channels are encoded by four different genes (HCN 1-4), but HCN2 is the most expressed isoform in the VTA. In a series of gene-based studies, we determined that overexpression of HCN2 in the VTA results in higher ethanol consumption and enhanced ethanol-induced locomotor activity, dopamine release, and place preference compared to control rats. On the other hand, the knockdown of gene expression of HCN2 in the VTA was associated with a marked reduction in voluntary ethanol intake in rats. In recent studies, we have found that the intracerebral administration of different HCN blockers ZD7288 (non-selective), MEL55A (moderately selective for HCN2), or 4e (highly selective for HCN2) to rats resulted in a marked dose-dependent reduction of the ethanol-induced dopamine release in the NAc, showing the selective HCN2 blocker 4e a higher potency. The neurochemical effects were correlated with a substantial reduction in the animal´s acquisition of voluntary ethanol intake. These results suggest that HCN2 ion channels may constitute a molecular target for the rewarding effects of ethanol.

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Alteration in glycine receptors in neurodegenerative diseases affects drinking behavior

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It is well known that alterations in cognitive and non-cognitive cerebral functions accompany Alzheimer´s disease (AD). Recent studies have implicated limbic regions, such as the nucleus accumbens (nAc) and the amygdala. Previous studies have shown the presence of inhibitory glycine receptors (GlyRs) in the nAc, whose activation is allosterically modulated by ethanol. Furthermore, in an earlier study using the APP/PS1 mice model (6-month-old), we found decreased GlyRs expression and function in the nAc. Our global working hypothesis is that GlyRs alterations in AD affect nAc functions and reward-related behaviors. We examined calcium homeostasis using the calcium fluorescent protein reporter GCaMP. To assay calcium-related signals, we electrically stimulated nAc and measured calcium responses using slice photometry. Increases in fluorescence were observed after adding the GlyRs antagonist (strychnine 1-4 µM). Interestingly, the effect of strychnine was significantly reduced in the APP/PS1 mice. Using patch clamp technique in brain slices, we compared GlyRs function and the modulation of GlyRs by ethanol, finding that ethanol potentiation was significantly decreased in AD mice. Finally, we performed drinking in the dark (DID) experiments and found that APP/PS1 mice consumed significantly less ethanol on the last day of DID, consistent with lower blood ethanol concentration. We discovered that APP/PS1 mice also had lower sucrose consumption. Collectively, these data support the critical role of GlyRs in nAc neuron excitability; decreased glycinergic activity in the APP/PS1 mice might lead to impairment in reward processing.

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Experimental approaches for studying ethanol-induced behavioral effects in Caenorhabditis elegans

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In addition to minor metabolic pathways, the enzymes alcohol dehydrogenases (ADHs) and aldehyde dehydrogenases (ALDHs) play a major role in ethanol biotransformation. Specifically, the ALDH superfamily is crucial for the detoxification of toxic aldehydes, not only acetaldehyde but also degradation products of biogenic amines such as DOPAL (3,4- dihydroxyphenylacetaldehyde), the first metabolite of dopamine. This has significant implications for various human conditions, including aging, neurodegenerative diseases, and cancer. Notably, many isoforms of ADH and ALDH are conserved across numerous organisms, including *Caenorhabditis elegans*. This invertebrate model recapitulates several alcohol-related behaviors that are modulated by the dopaminergic system, such as ethanol's stimulant and motivational effects. Building on these insights, this presentation will showcase data on ADH and ALDH activity, protein expression, and oxidative stress biomarkers in *C. elegans* transgenic strains under conditions of enzyme inhibition and activation. At the behavioral level, the study will examine ethanol-induced locomotor activity, positive chemotaxis, and basal slowing response (BSR), an adaptive mechanism reliant on dopamine functionality. Additionally, optogenetic approaches targeting the dopamine-containing neural circuit will be discussed in the context of ALDH inhibition. Lastly, a genetic cross in *C. elegans* will enable the visualization of ALDH in dopaminergic neurons using confocal fluorescence microscopy. Overall, these findings emphasize the role of key ethanol-metabolizing enzymes in physiological and pathological processes. They also highlight *C. elegans* as a promising new approach methodology (NAM), providing a reliable experimental model to investigate critical aspects of toxicant responses due to its high genetic homology with mammals.

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Chronic intermittent ethanol (CIE) exposure and stress induce elevated voluntary ethanol intake in C57BL/6J mice

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Alcohol use disorder (AUD) is a condition associated with compulsive/habitual alcohol drinking, loss of control over intake, and a negative emotional state when alcohol is not available. The development of animal models has been valuable in advancing 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 prevent relapse. Chronic intermittent ethanol (CIE) vapor exposure results in a significant increase in voluntary alcohol intake in male and female mice. CIE exposure also promotes tolerance to the aversive eFects of alcohol and insensitivity to the devaluation of alcohol reward. The translational potential of this model has been explored using drugs already approved to treat alcoholism (e.g., topiramate, naltrexone, and disulfiram). In addition, stress exposure has been identified as a risk factor for alcohol use disorder (AUD) that may induce higher levels of consumption. Several animal models have evaluated the eFect of stress on voluntary ethanol intake with mixed results. Work conducted in the INIAstress consortium has shown that repeated exposure to forced swim stress (FSS) induces a significant increase in voluntary alcohol intake in mice that had experienced repeated cycles of (CIE) vapor exposure. This eFect is selective for CIE-exposed mice since control (air-exposed mice) do not show a change in alcohol intake after FSS. This protocol has also been used to evaluate the therapeutic potential of various pharmacological agents that can reduce stress-induced drinking. Finally, recent studies show that mice repeatedly exposed to CIE exposure alone or in combination with stress continue to drink alcohol at a high level when sucrose is available as an alternative reward choice. The goal of these studies is to determine whether behavioral inflexibility contributes to the excessive voluntary alcohol intake observed in mice that experience both CIE exposure and stress. Results obtained with these mouse models could promote clinical investigations regarding the treatment of excessive drinking in the context of alcohol dependence and stress experience.

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Influence of emotional contagion on alcohol intake in rats

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Emotional contagion is a primitive affective tool through which an individual can synchronise their physiological and behavioural state with those of others. Depression, a mood disorder that affects an estimated 3.8% of the global population and is determined by two main clinical symptoms: depressed mood and anhedonia, can be contagious. Depression and anxiety disorder exhibit comorbidity with alcohol use disorder. After inducing depression-like symptoms in female Wistar rats (Rattus norvegicus) using reserpine, a monoamine depletor, the behaviour and alcohol consumption of animals (socials) that lived with them, for a period of 60 days, was evaluated. Social animals exhibited lower locomotor activity in the Open Field test and spent less time swimming in the Modified Swimming Test than controls, while also consuming more alcohol on days 4 and 7 out of the 10 sessions carried out. BDNF levels in the prefrontal cortex were decreased in reserpine and social animals. Reserpine animals improved their locomotor activity and exploratory behaviour in the Open Field test, and increased their swimming times in the Modified Swimming test after consuming alcohol. In conclusion, these results suggest the possible occurrence of an emotional contagion process and its plausible influence on the consumption of substances such as alcohol.

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Ethanol's mother mayhem: how environmental enrichment flips the script via oxytocin

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Environmental enrichment (EE) is a form of environmental manipulation where animals are exposed to various stimuli to promote social interaction, cognitive enhancement, and physical activity. Our research demonstrates that EE can modulate the oxytocinergic system, including increasing OT levels and mRNA expression in the hypothalamus, while downregulating OT receptor binding and phospholipase C (PLC) activity in specific brain regions. In our recent study, we exposed pregnant females to EE in the context of ethanol treatment to investigate whether EE could influence maternal care behavior, given the opposite effects of EE and ethanol on the OT system. Overall, dams in the standard housing-ethanol group exhibited a range of deficits in maternal care, which were mitigated by EE exposure. Ethanol-treated mothers showed reduced plasma OT concentrations, whereas those exposed to EE displayed an increased number of OT-immunoreactive cells in the paraventricular nucleus (PVN) and higher OT gene expression. Offspring of the standard housing-ethanol group, regardless of sex, exhibited delayed physical and reflex development and reduced social interaction. Female offspring showed increased ethanol consumption, reduced maternal aggression, and lower locomotor activity, while males exhibited heightened aggression compared to their EE-exposed counterparts. These detrimental effects were alleviated when the dams were exposed to EE during pregnancy (EE housing-ethanol offspring). This suggests that ethanol harmful outcomes were attenuated by EE exposure during pregnancy, highlighting the significant interaction between environmental factors and ethanol during gestation.

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Potential effect of alcohol consumption on alternative splicing during rat brain developing

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Prenatal alcohol consumption leads to alterations in neurodevelopment that manifest as fetal alcohol spectrum disorder (FASD). Within the FASD phenotype, we can observe facial abnormalities and changes in mental function that persist into adulthood. Alternative splicing increases the complexity of the neuronal proteome and consequently regulates the establishment and maintenance of neuronal development and synaptic plasticity. Bioinformatics studies conducted in our laboratory reveal that alcohol exposure alters the expression of splicing variants of synaptic and post-transcriptional regulatory functions, both in humans and animal models. These molecular events influenced by alcohol are observable in the short term rather than in the long term. We evaluated mRNA expression of splicing factors in the hippocampus and prefrontal cortex, 6 and 24 hours after alcohol exposure on of 7 days old rats. We found a time- and tissue-dependent expression specifically of the splicing factors (SF) SRRM4 and SRRM3. Currently, we are analyzing how these changes affect exon retention pattern in splicing variants, targets of these SFs, and their subsequent impact on cognitive alterations in FASD.

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Placental decidual vascularization and angiogenic determinants as predictive diagnosis of potential disruption of morphological feto-placental axis induced by perigestational alcohol consumption in a FASD-experimental model

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Placenta determines the fetal development and the origin of postnatal health and disease effects (DOHaD), particularly a placenta-brain axis has proposed to be intimate related. For fetal growth integrity, adequate supply of maternal blood to the fetal intervillous space depends directly on the establishment and development of the maternal uteroplacental vascularization (calibre, arrangement and histo-structure of maternal arterial vessels). The prenatal origin of FASD after maternal alcohol consumption may be associated with placental maternal vasculopathy. The effects of perigestational alcohol consumption (PAC) on fetal development-placental axis have not been established. Female mice were treated with 10 % ethanol in drinking water before and up to day 10 of gestation (TF), and control females (CF) were given ethanol-free water for the same periods. At day 13 of gestation, TF had reduced placental weight and area thickness (PAS-histomorphometry, ImageJ) vs CF. Although the maternal decidual area/ placental area (mm 2) in TF did not change, high abnormal histomorphological decidual stroma and endothelium, and increased decidual arteriole Nr (vascular density) and vascular area (vascular volume) were observed in TF-placentas vs CF. Concomitantly, the TF-fetuses % with craniofacial abnormalities and abnormal decidua increased 10 times vs CF. Analysing decidual angiogenic factors, uNK cell Nr (DBAlectin+) and VEGF expression (immunohistochemistry, ImageJ densitometry) were increased vs CF (p<0.05).These results show a relation between fetal anomalies, compatible with FASD, and the maternal decidual angiogenic-vascular disruption in the placenta after PAC. The placental monitoring studies in human (ecoDoppler) may be potentially useful for prenatal diagnosis of FASD.

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Exercise reduces physical alterations in a rat model of fetal alcohol spectrum disorders

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Prenatal alcohol exposure (PAE) induces neurodevelopmental adaptation and promotes a spectrum of behavioral disabilities. Children may show intellectual and neuromuscular problems, but their consequences or treatment are completely unknown. We aimed to investigate whether exercise intervention mitigates muscle and brain dysfunction in adolescent PAE offspring.

CTRL and PAE Sprague-Dawley male offspring were trained in 3 different exercise protocols for 4 weeks: Enrichment environment (EE), Endurance exercise (EEX), and Resistance exercise (REX). After interventions, we evaluated agility, strength, coordination, balance, and cognitive abilities, followed by measurement of plasmatic FNDC5/Irisin levels and neural and inflammatory markers through RT-qPCR in the hippocampus.

Results show that early adolescent PAE animals have significant alterations inagility and strength, without alterations in balance and coordination, compared toCTRL animals. EE significantly improved the strength in the PAE group but not in the CTRL group whose strength parameters were maintained even during exercise. REX was more effective for strength gain improvement than EEX, compared to CTRLs. However, REX failed to improve cognitive abilities in the PAE group, consistent with unchanged expression of plasmatic levels of Irisin, and hippocampal BDNF mRNA. Interestingly, in the PAE group and not in CTRL REX decreased the expression of IL-1β mRNA.

Our data suggests that individualized, scheduled, and supervised training of resistance is more beneficial than EEX or EE exercise for adolescents with FASD and highlights regulation of the neuroinflammatory status as a molecular target of exercise on brain function.

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Progressive alcohol abstinence: a strategy to counteractthe negative effects of paternal alcohol consumption onreproductive health

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Ethanol consumption can significantly impact sperm chromatin and, consequently, have severe effects on reproduction. Previously, we observed that male ethanol consumption led to sperm and testicular alterations, negatively affecting fertilization kinetics, embryo quality, and the reproductive health of male offspring. This study analyzed the effect of different abstinence periods from moderate paternal ethanol consumption as a potential therapy to reverse its impact on sperm. Male mice (Mus musculus, CrlFcen:CF1) were exposed (treatment group, T) or not (control group, C) to 15% ethanol in drinking water ad libitum for 12 days. Afterward, the mice were divided into three groups based on abstinence duration: 35, 70, or 105 days (representing 1,2, or 3 spermatogenic cycles). Spermatozoa from the epididymal cauda were assessed for motility, count, oxidative stress, plasma membrane integrity, and head decondensation. We found significantly lower motility in the T group at 35and 70 days of abstinence ($p = 0.0001$, $p = 0.0275$, respectively). Sperm count was also lower in these groups ($p = 0.0375$, $p = 0.0266$, respectively). Oxidative stress was increased at 35 days of abstinence ($p = 0.001$). Plasma membrane integrity was reduced at 35 and 70 days of abstinence ($p = 0.0321$, $p = 0.0017$). Head decondensation was higher in the 35-day T group ($p = 0.015$). No differences were found between C and T groups at 105 days of abstinence. These results suggest that an abstinence period longer than two spermatogenic cycles may reduce the negative effects of alcohol consumption.

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Gestational environmental enrichment attenuates theeffects of pre- and postnatal ethanol exposure: contribution of oxytocin and hevin

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The maternal-offspring relationship during gestation is susceptible to external factors, such as ethanol exposure, which can impair maternal behaviors critical for the development and survival of the offspring. This study aimed to evaluate the effects of ethanol exposure during the neurodevelopmental period and gestational environmental enrichment (EE) on both mothers and their offspring. We assessed maternal behavior, anxiety-like behavior, and the expression of oxytocin (OT) and its receptor in the hypothalamus. Additionally, we examined hevin, a protein involved in synaptic plasticity and cognitive functions, in the medial prefrontal cortex (mPFC) of male pups. Female Swiss mice were randomly assigned to four groups: housed in standard cages and treated with water (CT) or ethanol (ETOH), or housed in EE for 3 hours/day and treated with water (EE-CT) or ethanol (EE-ETOH). Gestational EE was provided during pregnancy, and ethanol treatment (3g/kg) was administered from gestational day 15 (GD15) to postnatal day 10 (PND10). The results revealed that ETOH-treated mothers displayed reduced maternal behavior, increased anxiety-like behavior, lower OT levels, and decreased hypothalamic mRNA expression of OT and its receptor. Notably, these deficits were absent in EE-ETOH mothers. Male pups of ETOH and EE-ETOH mothers exhibited reduced hevin expression in the anterior cingulate and infralimbic cortex, though EE increased hevin expression in the infralimbic cortex. This study demonstrates that gestational EE can mitigate ethanol-induced impairments in mothers by modulating OT and its receptor in the hypothalamus, potentially preventing deficits in maternal and anxiety-like behaviors, and in offspring through the regulation of hevin expression in specific mPFC sub-regions of male pups.

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Prenatal ethanol exposure and adolescent restraint stress induce a perseverative phenotype in wistar rats

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Introduction: Early exposure to prenatal ethanol favors the development of psychopathological disorders. It is unclear, however, how this exposure interacts with other developmental insults.
Objective: The objective of this study was to evaluate the synergistic effects between prenatal ethanol exposure and adolescent stress on repetitive and/or perseverative behaviors in male and female Wistar rats.
Methods: On gestational day (GD) 17-20, pregnant female Wistar rats received i.g. administrations (0.0 g/kg/d or 2.0 g/kg/d of ethanol). On postnatal day (PD) 32-34, the male and female offspring were exposed to restraint stress or control conditions, while on PD 36-41, they were evaluated in the marble burying test and the perseveration test. In the latter the rats are introduced in an arena containing 4novel objects. Shorter average return time to a given object suggests compulsive checking behavior.
Results: The male rats prenatally treated with ethanol and exposed to stress (a) buried significantly more marbles than controls and (b)exhibited, in the perseverance test, a significantly shorter average return time to object 1 compared to controls (p<0.05). Likewise, females treated with ethanol but not exposed to stress exhibited greater marble burying compared to the other groups of the same sex (ps<0.05).
Conclusions: These results are indicative of a repetitive or compulsive behavior phenotype in males exposed to prenatal ethanol and adolescent stress, supporting our hypothesis that the two-hit associated with these developmental insults could trigger the induction of early psychopathology.

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Semichronic paternal alcohol intake leads to peri-implantation embryo development dysregulation via potential morphofunctional sperm defects induced by oxidative-proinflammatory testicular-epididymal state

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Recently, we demonstrated in mouse that semichronic paternal alcohol consumption (SPAC) alters the fertilization and male pronuclear development dynamics. However, the effects of SPAC on preimplantation embryonic competence and the implantative blastocyst development, and its probable link with sperm morphofunctional disruption due to induction of oxidative-proinflammatory gonadal state have not been well explored. Adult CF1 male mice were treated with ethanol 15%/drinking water for 15 days (MT), and controls were given water alone (MC). MC and MT were mated with normal females and their pregnancy continued until day 2 (D2) or day 4 (D4) of gestation for embryo isolating, and caudal spermatozoa, testis and epididymides were dissected from mated MC and MT. At gestational D2 andD4, the % of 2-cell embryos and expanded blastocysts, respectively, decreased in MT-mated females vs controls ($p<0.05$). During the in vitro implantation, embryo growth and differentiation from MT-mated females were severely deregulated while altered ICM and trophectoderm. MT had increased abnormal spermatozoa % (H&E) and decreased vitality (Eosin test) vs MC ($p<0.05$), suggesting adverse effects of ethanol on testicular spermatid differentiation and sperm functional acquisition in the epididymis. Next, in MT we observed high oxidative induced-protein nitration (immunohistochemistry for nitrotyrosine) and significant increased number of proinflamatory mastocysts (Alcian Blue technique) in testicular seminiferous tubules and epididymides ($p<0.05$) vs controls. In conclusion, SPAC leads to altered regulation of dynamics of peri-implantation embryo development probably via dysmorphofunctional sperm defects produced by generation of oxidative and proinflammatory testicular-epididymal state during ethanol exposure.

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Sustained neuroinflammation in littermates prenatally exposed to alcohol

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Prenatal alcohol exposure affects up to 3% of live births with the Central Nervous System as one of the most vulnerable targets. To assess the effects of acute maternal alcohol consumption when neurons and glial cells are formed, Sprague Dawley rats were exposed to 6 g/Kg ethanol plus 5% sucrose in the drinking water during the 12 up 15 days of gestation or with drinking water alone or 5% sucrose (controls). At the birth, rat pups were counted and weighted until processing at 1, 3, 15 and 30 postnatal days. Neuronal damage, glial reactivity and neuroinflammation markers were determined in CNS samples. Inflammation markers and effectors were assessed in serum and liver samples. No significant effects in the number and weight of animals, neither on neuronal viability, were found in rats from ethanol mothers related to controls. However, hippocampal glial reactivity persisted as mild increases in GFAP immunoreactivity or tomato lectin labelling or significantly increased S100β up to 30 postnatal days. Similarly, increased TNF-α and interleukin-1β gene expression was found at 30 days in the ethanol condition related to controls. The inflammation effector, matrix metalloproteinase 9 increased around a week after the birth. Results obtained suggest that a short-time maternal exposure to high alcohol was sufficient to elicit inflammation in the whole descendency that persisted 30 days upon the birth. Future work will compare the effects of maternal alcoholism in function of rat pups sex as well in young adults.

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Serotonin and metabolic ethanol effects on ventilatory response to intermittent hypoxia in rat neonates

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Early EtOH high/acute doses diminish hypoxic ventilatory response and serotonin-5HT levels in the medullary 5HT-system. Yet, differential effects of EtOH pre-exposure from those of acute EtOH intoxication during delivery/neonatal period have not been studied. Here, we studied whether EtOH pre-exposure together or not with an acute EtOH intoxication alters ventilatory, metabolic and neurochemistry response against an intermittent hypoxic challenge (IH). At postnatal days-PD 3, 5and 7, pups were pre-exposed to EtOH or vehicle (2.0 or 0.0g/kg, ig). At PD9, pups were EtOH re-intoxicated or not (vehicle-administered) and all pups were subjected to a IH protocol (O 2 8%). Respiratory frequencies (fR) were recorded in a whole body plethysmograph. After, brains and blood samples were collected. 5TH-neurons in medullary raphe nuclei and metabolic hypoxemia/hypercapnia parameters we reassessed.

Results showed that acute EtOH intoxication depressed breathing, particularly during hypoxic events, independently from EtOH pre-exposure. Yet, in sober pups, EtOH-exposure increased fRs during hypoxic events. After IH, acute EtOH-intoxication induced a metabolic acidosis-hypercapnia but EtOH pre-exposure increased pO 2 ,SO% and COHb/oxyHb ratio. Any form of EtOH exposure increased 5HT levels in medullary raphe nuclei analyzed.

In summary, EtOH pre-exposure induces different effects from those generated by acute intoxication itself. In acute, respiratory depression with hypercapnia/acidosis was found. However, EtOH pre-exposure improves ventilatory and oxygenation patterns. Probably, acute intoxication masks EtOH pre-exposure effects, which are only appearing under sobriety. However, any form of drug experience increases 5HTlevels in the medullary raphe nuclei.

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Impact of alcohol exposure on intestinal permeability and adolescent alcohol consumption

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Prenatal alcohol exposure (PEE) has been related to several neurobiological and cognitive impairments in the offspring. This experiment aimed to elucidate the mediating role of the microbiota on the effects of PEE, specifically regarding to alcohol intake and behavioral outcomes during adolescence.

On gestational day 9, C57BL/6 mice were subjected to binge alcohol consumption (0 vs. 10% concentration) exposure via a drinking in the dark (DID) protocol, from gestational day 9 to postnatal day 5, four days per week, 2 or 4 hour per session. On weaning day, colon samples were collected from the offspring, to measure the gene expression of several intercellular junction proteins, via rtPCR, which contribute to intestinal integrity and permeability. Anxiety-like behavior, locomotor activity and alcohol consumption were also assessed in early adolescent male and female offspring.

Pregnant females consumed an average of 2.13 and 1.82 g/kg of alcohol in the second and third weeks of pregnancy, respectively, and 4.32 g/kg during the first postnatal week. The results indicated a trend toward reduced gene expression of occludin and claudin in the colon of alcohol-exposed offspring. Additionally, the alcohol-exposed offspring exhibited heightened alcohol intake compared with control pairs.

The present results suggest that PEE could potentially lead to higher intestinal permeability, facilitating the transport of inflammatory molecules to the central nervous system. This phenomenon could ultimately explain the increased alcohol consumption in adolescence in this and other preclinical models of PEE.

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Omega-3 (ω-3) fatty acid effects on anxiety-like behavior and oxidative stress in a binge-like ethanol exposure model in adolescent rats

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Alcohol consumption is a worldwide concern that causes 5% of the global disease burden being adolescents among the most vulnerable to its negative effects. Previous evidence suggests that alcohol exposure increases anxiety-like behavior (AnxB) and oxidative stress (OS) while ω-3 can revert these effects. Yet, no literature was found about these outcomes in adolescence. The aim of this study was to analyze the long-term effects of binge-like EtOH exposure and DHA treatment on behavior and OS in adolescent Wistar rats. We administered 2 or 0g/kg of EtOH (ig) at postnatal days (PD) 28, 30 and 32. 15 min after, animals received DHA (1 or 0mg/kg, ip). At PD 34 subjects were evaluated in the Light-Dark Box for 5 min to assess AnxB. At PD 35 blood and tissue was collected to measure OS by measuring thiobarbituric acid reactive substances and catalase activity in different brain areas. DHA treated animals spent less time in the dark compartment (p=.043) and had decreased catalase activity in Prefrontal Cortex (PFC) (p=.012). EtOH+DHA animals had lower TBARS levels compared to the Water+DHA group (p=.041). Moreover, AnxB correlated with catalase activity in Motor and PFC (.52 and .37) and TBARS levels in EtOH+Albumin rats (.82). These results suggest that DHA can beneficially decrease AnxB and OS in adolescent rats. We found no significant effect of EtOH exposure. This may be because the evaluations were carried out on sober animals that were exposed to the drug several days before.

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Evaluation of negative affect behaviors following chronic exposure to alcohol vapor in male C57BL/6 mice

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Our study aimed to evaluate whether chronic exposure to ethanol vapor could induce negative affect behaviors (NAB). C57BL/6 male mice (CEUA 3810070823) were subjected to a chronic intermittent ethanol vapor and two bottle choice paradigms (CIEV-2BC) to induce ethanol dependence and withdrawal behavior. Mice were allocated in three groups: AIR (n=9), CIE (n=5) and Naïve (n=6). After the last vapor exposure, the animals underwent, at different times, to the elevated plus maze test (EPM); Light/Dark Box (LDBOX); Novelty-suppressed feeding (NSF); Marble burying (MB); Bottle brush (BB); Sucrose preference (SP) and Social investigation (SI) tests. For the EPM test, the CIE group spent less time in the open arm than the AIR group. For the number of entries into the open arm, the CIE group had fewer entries than other groups. LDBOX test, for the latency to enter the light compartment, the CIE group had a longer latency time than the AIR group. In the NSF test, for the latency time to seek food in the center of the arena, the CIE group had a longer latency time than the other groups. MB test, the CIE group buried more marbles than other groups. BB test, the CIE group showed more defensive behavior than the other groups. SP test, there was no difference in sucrose consumption between the groups. SI teste, there was no difference in time in the interaction zone between the groups. Our findings corroborated the literature data showing that CIEV induces symptoms of NAB during the acute withdrawal period.

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Environmental enrichment as a tool to blunt the sensitization process in mice exposed to alcohol consumption

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The sensitization process is crucial in alcohol use disorder, a complex disease where repeated alcohol exposure leads to neuroadaptations, resulting in an increased pharmacological and behavioral response, even at lower alcohol doses. In order to understand these behaviors related to alcohol consumption, animal models are often used, even to assess whether sensitization occurs. Between the criteria used to assess sensitization is an increased locomotor activity following alcohol administration. However, environmental manipulations in housing, designed to enhance locomotor, cognitive, and social parameters, known as Environmental Enrichment (EE), can inhibit the sensitization process, reducing locomotor activity in mice. This study aimed to determine whether the reduction in sensitization is due to cognitive and social enhancements mediated by EE or merely physical exercise. In order to investigate it, Swiss mice were divided into four groups: EE housing with a running wheel, EE without a running wheel, standard housing with a running wheel, and standard housing without a wheel. After habituation, the animals underwent a 15-day alcohol administration protocol, followed by a 7-day alcohol-free period. On the 22nd day, a test was conducted where the mice were exposed to alcohol, and their locomotor activity was recorded and analyzed. The results showed that the groups with a running wheel exhibited a sensitization response, as well the EE group. Nevertheless, the EE group demonstrate a reduce to locomotor activity after the sensitization, showing it may be applied as a tool to reverse sensitization.

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Parenting conditions modulate adolescents anxiety, social behavior and oxytocin neural response

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Social attachment plays an important role in progeny development. Different social experiences during lactation and throughout life can affect offspring behavior and, in turn, alcohol response. We aimed to analyze if different parenting conditions (single-mother, SM, or biparental, BP, parenting), in C57BL/6 mice, may have a differential impact on adolescent anxiety, social behavior, and oxytocinergic (OT) neural response. Mice were reared in a SM or BP structure. Adolescents from both parenting conditions were evaluated at postnatal day (PD) 28 in the Elevated Plus Maze (EPM) and after their brain was perfused for OT immunofluorescence. Other adolescents were tested in a social interaction test. For the EPM, mice received an injection of ethanol at doses of 0.0 or 2.0 g/kg. For the social interaction test, subjects were injected with a dose of 0.0, 0.5, or 2.0 g/kg ethanol. Analysis of adolescent behavior indicated that SM subjects displayed more anxiogenic-like behaviors and fewer social activities than BP adolescent mice. Ethanol at 2.0 g/kg induced anxiolysis in SM adolescents. Furthermore, BP adolescents have significantly more OT in hypothalamic neurons. In conclusion, single-mother parenting induces greater anxiogenic and lower social behavioral profile in comparison with a biparental structure. Moreover, changes in oxytocin neurons could help to elucidate the mechanism underlying parenting differential effects.

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Maternal enrichment, ethanol exposure and FASD: insights into maternal care, oxytocin modulation and offspring behavior

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Ethanol consumption during pregnancy and lactation may result in a range of neurodevelopmental consequences in offspring, associated with fetal alcohol spectrum disorders (FASD). Additionally, it may impact on maternal behavior, possibly due to a decrease in oxytocin (OXT) release. However, environmental enrichment (EE) appears to improve maternal care and modulate the oxytocinergic system. This study evaluated the effects of EE on maternal care of mice exposed to ethanol as well as on offspring behaviors and development. Female Swiss mice were divided into four groups: standard housing-water; standard housing-ethanol; EE housing-water and EE housing-ethanol. EE occurred during gestation, and dams were treated from gestational day 15 to postnatal day (PND)10. Maternal care was evaluated on PND4 before daily treatment. OXT-immunoreactive cell count in hypothalamic paraventricular nucleus, and OXT gene expression in the hypothalamus were assessed in dams after weaning. Physical and reflexological development, ethanol intake, social interaction in adolescence, and aggressive behavior in adulthood were evaluated in offspring. Dams in standard housing-ethanol group exhibited reduced maternal care, which was mitigated by EE. Furthermore, an increase in OXT- immunoreactive cells and OXT gene expression was observed in dams exposed to EE. Regarding the offspring, ethanol-exposed males and females exhibited delayed development and reduced social interaction. Females showed increased ethanol consumption and decreased maternal aggression, while males displayed elevated aggressive behavior. However, these effects were not observed in offspring also exposed to prenatal EE. The results showed that ethanol disrupts maternal care and offspring development but the effects may be attenuated by maternal EE.

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Acute ethanol exposure in C. elegans: a behavioral approach

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Among other factors, acute ethanol (EtOH) toxicity depends on its oxidative metabolism. The present work sought to characterize an experimental model in *C. elegans*, a nematode that can recapitulate several EtOH responses. Psychoactive EtOH-relevant doses were selected by measuring lethality and locomotor activity. Worms from the Bristol N2 (wild-type) and RB2114 (null mutant for sodh-1 -adh in humans) strains were maintained at 20°C in the Nematode Growth Medium (NGM) medium until they reached the L4 stage (adults). Wild-type N2 animals exposed to 0-500 mM EtOH for 1 h were transferred to an agar plate to determine the mortality by manual counting. The survival of N2 nematodes was greater than 98% at all the EtOH doses evaluated. For locomotor assays, the N2 and the RB2114 strains were exposed to 0 or 500 mM EtOH for 1 h and the speed and distance traveled were recorded using the MicroTracker software. As expected, both strains exposed to EtOH showed less activity than controls. Finally, ADH (SODH-1) functionality was assessed in both strains through the acrolein survival assay by exposure to 0.05 mM allyl alcohol. A significantly higher survival in response to allyl alcohol was observed in the RB2114 strain compared to N2 animals. These results demonstrated that 500 mM EtOH corresponds to a sublethal sedative dose sedative in the exposed animals. In addition, a remarkable attenuation of SODH-1 activity was confirmed in the RB2114 strain, a situation that will be explored in future studies to provoke EtOH accumulation in the body.

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Positive and negative pathways connecting depressive symptoms to alcohol misuse in argentine college students: a study of urgency traits and internal drinking motives

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Introduction: Different theoretical models describe the relationships between personality traits, drinking motives, and alcohol-related outcomes. One proposed sequence suggests that internal drinking motives, combined with negative and positive urgency (i.e., the tendency to act impulsively under intense positive or negative emotions), link depressive symptoms to alcohol-related problems. This sequence has rarely been analyzed in Latin American samples.

Objective: To evaluate a sequential model, in a sample of 403 Argentinian university students (68.2% women; Mage=21.03±4.90), that connects depressive symptoms, urgency traits, internal drinking motives, and problematic alcohol use.

Methods: A path analysis examined the direct and indirect relationships between depressive symptoms and alcohol outcomes (e.g., heavy episodic drinking and alcohol-related negative consequences), via urgency traits and internal drinking motives.

Results: Indirect pathways were found linking depressive symptoms to problematic alcohol use through urgency traits and drinking motives (e.g., depressive symptoms → positive [negative] urgency → enhancement [coping] motives → drinking problems).

Conclusions: The proposed sequence received empirical support in this specific sample of Argentinian adults. The findings suggest that students experiencing more depressive symptoms may be more prone to heavy drinking and alcohol-related problems, as a result of acting impulsively during intense emotional states and using alcohol to regulate mood. Future interventions to prevent or reduce problematic alcohol use, particularly among Argentinian young adults, should consider targeting these impulsivity traits and affect-related drinking motives.

Keywords: *symptoms of depression, urgency traits, drinking motives, problematic alcohol use, college students*

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Patterns of THC use and socio-cognitive factors of users across cannabis sources in Uruguay

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Introduction: There is interest in how the transition from an illegal to a legal THC (Tetrahydrocannabinol, the psychoactive component in cannabis) market affects consumer behavior, and the characteristics of consumers associated with the different drug sources. In 2013, Uruguay became the first country to fully legalize cannabis, allowing THC commercialization through three outlets: home cultivation, cannabis clubs (groups of 15-45 members who can grow cannabis collectively and share the harvest), and pharmacies.
Objective: To examine patterns of THC use associated with each outlet type in Uruguay and socio-cognitive factors influencing drug use.
Methods: A sample of 1,066 Uruguayan adults (639 women, mean age = 24.9±3.51 years) who used THC in the last month completed a survey assessing their preferred THC source, frequency and quantity of use, psychological distress (Kessler scale), negative consequences, protective behavioral strategies (PBS), and motives for use.
Results: Cannabis clubs were the preferred legal source of THC (25.7%), though surpassed by ”Other” sources (34.05%). THC frequency and consumption were higher among club users compared to those obtaining it from pharmacies or other sources. Users of “Other” sources reported greater psychological distress than any other group. Negative consequences and PBS usage were similar across groups, while those relying on ”Other” sources endorsed the fewest enhancement motives.
Conclusions: Despite the availability of legal outlets, alternative sources, likely including the black market, remain significant in Uruguay. Cannabis clubs, the most popular legal source, were associated with higher THC use, highlighting the need for targeted prevention efforts for these users.

Keywords: *THC, legal outlets, Uruguay, marihuana problems, PBS*

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Establishment of IA2BC voluntary ethanol consumption paradigm in sprague dawley rats

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The availability and reproducibility of models of alcoholism are paramount and can be hindered when alcohol preference is directly linked to their inbred status. Utilizing outbred animals that are readily available would open the door to more reliable studies. This study evaluated the intermittent access two-bottle choice (IA2BC) binge drinking paradigm in Sprague Dawley rats to assess its ability to produce pharmacologically relevant blood alcohol levels. Twenty Sprague Dawley rats (10 females, 10 males) were exposed to the IA2BC paradigm for five weeks, during which two alcohol solutions (10% and 20%) were provided alongside water for 24 hours on three non-consecutive days each week. A control group received only water. After five weeks, the rats underwent a one-week abstinence period with no alcohol access. During this period of abstinence, were recorded to capture behavioral abstinence effects, followed by reintroduction to alcohol to monitor relapse consumption. Blood alcohol levels were measured at the end of the initial five-week period and post-abstinence.

Results showed that alcohol consumption peaked at 2.5 g/kg in females and 0.3 g/kg in males by the fifth week. Upon reintroduction, peak consumption increased to 4 g/kg in females and 1.9 g/kg in males, stabilizing at 1.9 g/kg and 1 g/kg, respectively. Alcohol intake quickly returned to baseline levels. Hepatic enzyme levels (ALT, AST, GGT) remained unaffected by alcohol consumption.

The study concluded that the IA2BC paradigm led to elevated alcohol intake in females but did not induce pharmacologically significant alcohol levels in Sprague Dawley rats overall.

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Selective expression of a high-velocity ADH enzyme in rat hepatoma cells driven by a minimal albumin promoter

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Ethanol is metabolized primarily by the enzyme Alcohol Dehydrogenase (ADH) to produce acetaldehyde, which is subsequently oxidized by Aldehyde Dehydrogenase (ALDH) to acetate. Blood accumulation of acetaldehyde generated an adverse body reaction to alcohol consumption. Specific polymorphisms of ADH and ALDH cause a higher production and/or a slower elimination of acetaldehyde, increasing the toxicity associated with this molecule. One of these variants is ADH1B*2, an enzyme 10-fold more active than the wild-type ADH1B*1, leading to an increased generation of acetaldehyde from alcohol. Indeed, ADH1B*2 carriers show a 50% lower incidence of alcoholism than the general population. Previous studies by Rivera-Meza et al. (2010) showed that administration of adenoviral vectors encoding a mutant rat ADH enzyme (rADH47His, analog of ADH1B*2) to UChB drinking rats resulted in an increase of blood acetaldehyde after alcohol administration and a reduction of voluntary alcohol consumption, similar to that observed in humans carrying ADH1B*2. The current investigation seeks to optimize the delivery of the rADH47His gene by developing an adeno-associated vector with lower immunogenicity and incorporating a minimal albumin promoter sequence so that expression is selective for hepatocytes. Vector modifications will be made by subcloning plasmids, and the constructs will be transfected into hepatocytes (line H4-II-E-C3) and non-hepatic cells (line HEK293). The activity of ADH and the selectivity of its expression will be tested in vitro by indirect ADH activity assays, and the production of acetaldehyde will be measured by HPLC. It is expected to obtain a hepato-selective vector for subsequent in vivo studies.

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Study of G protein-coupled receptor kinase 2 and D2 receptor levels in a novelty seeking behavior

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Drug addiction is characterized by the repeated use of drugs despite their adverse effects. However, not all individuals develop drug addiction. A behavior that predicts susceptibility to drug addiction is novelty seeking. Rats with high novelty- seeking (HR) behavior are more prone to develop addiction compared to those with low novelty-seeking (LR) behavior. In HR rats, the expression of dopamine type 2 receptors (D2R) is lower than in LR rats. However, the mechanism underlying the low D2R levels in HR subjects remains unclear. D2Rs are G protein- coupled receptors (GPCRs) regulated via desensitization and internalization by G protein-coupled receptor kinases (GRKs). But it is unknown whether GRKs play a role in novelty-seeking behavior. In this research, we aim to determine the levels of D2R protein and GRK2 in the HR/LR model. Adult male Sprague Dawley rats will be subjected to a novelty-seeking test in an open field. Subsequently, tissues will be extracted to obtain the cytosolic and synaptosomal fractions from the dorsal striatum (DS). Western blots will be performed to quantify the levels of D2R and GRK2. Our results indicate that GRK2 levels are significantly higher in HR rats than in LR rats, which is accompanied by lower D2R levels in HR rats. Both findings were only observed in the synaptosomal fraction. These results suggest that high novelty-seeking rats exhibit elevated GRK2 levels, suggesting that the decrease in D2R levels in HR rats is modulated by GRK2.

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Identifying GLT1-inducing molecules in MSC-secretome for alcohol use disorder treatment

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Alcohol Use Disorder (AUD) is characterized by persistent, excessive alcohol consumption despite negative consequences. Human and animal studies indicate that chronic alcohol intake leads to neuroinflammation, which result in hypertrophy of astrocytes and reduction of astrocyte glutamate transporter GLT-1 levels, leading to increases in extracellular glutamate levels in the tripartite synapse, intensifying cued dopamine effects and enhancing voluntary ethanol intake. While effective treatments for AUD remain limited, MSC-secretome has emerged as a promising therapeutic approach. Studies have shown that MSC-secretome can reduce alcohol intake and relapse in rodent models primarily by upregulating GLT- 1. The dependence of therapeutic effects on GLT-1 is further supported by the complete inhibition of these effects following GLT-1 antisense administration. Therefore, our goal is to identify molecules within the MSC-derived secretome that can induce GLT-1 expression and disrupt the addictive cycle.

To identify GLT-1-inducing molecules in MSC-secretome, a comprehensive analysis was conducted. Bioinformatics tools identified several candidate molecules, which presence in the MSCs and in the MSC-derived secretome was validated using RT-qPCR and ELISA respectively. Intranasal administration of liposomes containing the selected molecules significantly decreased alcohol consumption at a similar level observed in animals treated with the intranasal administration of the complete MSCs-derived secretome. We propose that these molecules could induce GLT-1 levels, reducing alcohol consumption in an animal model of voluntary alcohol intake, suggesting their potential therapeutic value for the treatment of AUD.

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Expression and gene knockdown by small hairpin RNA of salsolinol synthase in vitro

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Ethanol-derived acetaldehyde can condense non-enzymatically with dopamine to generate racemic (R/S)-salsolinol and enzymatically to generate (R)-salsolinol. This molecule has been shown to activate the mesolimbic system, suggesting that it mediates ethanol´s rewarding and reinforcing effects. Specifically, the (R) enantiomer has been associated with motivational effects, behavioral sensitization, and increased ethanol consumption. Due to the neurotoxic capacity of salsolinol and its metabolites in dopaminergic neurons, the enantioselective enzyme involved, salsolinol synthase, was recently isolated and sequenced. However, the precise role of salsolinol synthase in alcohol addiction is not yet fully understood. The aim of this study is to validate salsolinol synthase as a pharmacological target for alcohol addiction. The mRNA expression was detected by RT-qPCR, protein expression through Western blot, and catalytic activity was assessed using HPLC- coupled electrochemical detection. HEK-293 cells were transfected with a plasmid encoding salsolinol synthase, while the endogenous expression was studied in PC- 12 and RCSN-3 cells. Subsequently, shRNAs targeting salsolinol synthase mRNA were designed and co-transfected with the plasmid encoding the enzyme to induce gene knockdown. The inhibitory efficacy was evaluated using the previously mentioned methods. These studies could validate the activity salsolinol synthase, and its gene knock down as a potential therapeutic strategy for alcohol addiction.

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Evaluation of the hepatoprotective potential of moringa (Moringa oleifera Lam.) Extract in the alcohol-induced toxicity in HepG2 cells

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Plants have been historically used to treat diseases, with many modern drugs tracing their origins to plant-derived molecules. Natural products have gained popularity for managing health issues in recent years, especially during the COVID-19 pandemic. However, despite a long tradition of medicinal plant use, studies of their efficacy and safety are still limited, especially for hepatoprotection in the case of alcohol liver disease. Many plant products, such as Moringa (Moringa oleifera Lam.), have been described and even advertised to be useful to prevent and treat alcohol-induced damage of the liver, despite the limited evidence and studies available for its use in alcohol liver disease. Thus, the objective of this study is to evaluate the safety and potential of Moringa oleifera Lam. in alcohol liver disease, especially for its most severe form, alcoholic hepatitis. In this study, two extracts of moringa were prepared using different concentrations of methanol, fully dried, and phytochemically characterized for their polyphenol and flavonoid contents using the Folin-Ciocalteu and AlCl3 assays, respectively, and their antioxidant potential using the Ferric-Reducing Antioxidant Power assay (FRAP). The toxicity of both extracts, prepared as aqueous solutions, in an increasing dose of 0 µg/mL to 200 µg/mL, was then evaluated in HepG2 cells using an MTS assay. Results have shown that solvent concentrations in extraction affect the final phytochemical composition, and while both extracts showed antioxidant activity, the results were different. The toxicity of the extracts in HepG2 also differs. Thus, proper solvent selection in extract preparation must be considered.

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Resveratrol attenuates ethanol-induced reproductive damage in male mice

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This study investigated the effects of ethanol consumption on sperm quality, testicular histology, and reactive oxygen species (ROS) levels, and whether resveratrol could reverse these effects. Adult male mice (Mus musculus, CrlFcen:CF1) were divided into four groups: Control (water + vehicle), Et (15% ethanol + vehicle), Res (water + resveratrol 20 mg/kg), and EtRes (15% ethanol + resveratrol 20 mg/kg). Ethanol was provided ad libitum in drinking water, and resveratrol or vehicle was administered via gavage every 24 hours for 12 days, followed by two days of water only. After sacrifice, sperm motility, concentration, viability, membrane integrity (hypo-osmotic swelling test), and ROS presence (CellROX Green assay) were evaluated. DNA fragmentation (TUNEL assay) and histological analysis (hematoxylin-eosin staining) were performed on testicular tissues. Sperm membrane integrity significantly decreased in the Et group compared to Control ($p<0.05$), with resveratrol showing a protective effect in EtRes group. No significant differences were observed in sperm concentration, motility, or viability among the groups. DNA fragmentation in seminiferous tubules and Leydig cells was significantly elevated in the Et group ($p<0.001$), with resveratrol reducing this damage in both the Res and EtResgroups. Histological analysis showed that resveratrol prevented ethanol-induced damage, including disorganization ($p<0.05$) and the presence of residual bodies ($p<0.01$) in the seminiferous epithelium. In conclusion, ethanol impairs sperm membrane integrity, increases DNA fragmentation, and disrupts testicular histology, with resveratrol partially mitigating these adverse effects.

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Preadolescent methylphenidate exposure modifies ethanol-induced motor stimulation in adult mice in a model of attention-deficit/hyperactivity disorder

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According to the World Health Organization, 2 billion people globally consume or abuse alcohol, causing 3.2% of deaths. Attention-Deficit/Hyperactivity Disorder (ADHD), the most common behavioral disorder in childhood, affects around 4% of children and impacts their social and academic functioning. The psychostimulant methylphenidate (MTPH) is the most commonly treatment for ADHD. Considering that MTPH has pharmacodynamics similar to amphetamine and that the risk of alcohol abuse and addiction are influenced by the age of onset of substance use and exposure, chronic MTPH use during childhood or adolescence may increase the likelihood of substance abuse in adulthood. We studied the effects of chronic MTPH treatment during childhood/adolescence on ethanol motor-stimulating effects in adulthood in an ADHD animal model. We used p35KO transgenic mice and wild-type (WT) controls, both chronically treated with MTPH from postnatal days 21-31 and tested for ethanol-induced stimulation and sensitization in adulthood. We found that p35KO- CON and MTPH treated mice exhibited ethanol-induced stimulation only after 14 days of repeated exposure, without developing sensitization, unlike the WT controls. However, only p35KO-MTPH-treated mice exhibited a sustained stimulant effect. In conclusion, our study underscores the critical role of the Cdk5/p35 complex in ethanol stimulant response. Also, we demonstrate that chronic psychostimulant treatment during preadolescence leads to a loss of the sensitization phenomenon, suggesting that prolonged MTPH treatment may pose a potential risk of addiction.

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Gut-microbiota-derived extracellular vesicles from animals genetically selected to prefer alcohol induce high alcohol intake in abstinent rats

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Objective: Emerging evidence suggests that gut microbiota may influence alcohol consumption. Extracellular vesicles (EVs) play a key role in bacteria-to-host communication, yet their potential role in addictive behavior remains unexplored. This study aims to investigate the role of gut microbiota-derived bacterial extracellular vesicles (bEVs) in high alcohol consumption.

Methods: Feces were collected from animals selected to prefer alcohol (UChB rats), both with and without previous alcohol consumption. bEVs were isolated, characterized, and injected (i.p.) into Wistar rats (known for rejecting alcohol). To assess the effect of bEVs on alcohol intake, animals were offered a three-bottle-choice between water, 10% ethanol, and 20% ethanol. Voluntary consumption was measured daily for four consecutive days, and on day four, the animals were euthanized, and tissues were collected.

Results: Both types of UChB-bEVs were capable of increasing Wistar's voluntary alcohol consumption by up to 10-fold ($p < 0.0001$), indicating that bEVs are able and sufficient to transmit drinking behavior across different rat strains. Neuroinflammation was observed only in animals receiving bEVs from UChB rats that had previously consumed alcohol, evidenced as microglial and astrocyte activation in the nucleus accumbens and prefrontal cortex. Finally, we demonstrate that the vagus nerve mediates the increase in alcohol consumption, as bilateral vagotomy completely abolished the bEVs-induced high drinking behavior.

Conclusion: This is the first study proposing gut microbiota-derived extracellular vesicles as a novel mechanism mediating high alcohol intake. Furthermore, we demonstrate that the isolated particles can transmit this reinforcing/addictive behavior between different rat strains, in a vagus nerve- dependent manner.

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HCN ion channel blocking as a strategy to avoid the rewarding effect of ethanol on rats

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The mesocorticolimbic system is a dopaminergic neurocircuit involved in the reinforcement of survival related activities, ethanol is capable to activate it, causing an increase in dopamine release from the Ventral Tegmental Area (VTA) to the Nucleus Accumbens (NAc), inducing a rewarding effect. The firing frequency of dopaminergic neurons in the VTA is regulated by HCN2 (hyperpolarization-activated cyclic nucleotide-gated) ion channels. Ethanol can increase their activity, and consequently, an increase in dopamine release in the NAc. Therefore, selective blockade of HCN2 channels holds potential as a novel pharmacological approach for treating alcoholism. In this study we synthesized a selective HCN2 channel blocker (4e). Three HCN blockers were evaluated: ZD7288 (non-selective), MEL55A (moderately selective for HCN2), and 4e (highly selective for HCN2). The reinforcement effect of ethanol was evaluated in two experiments. In the first experiment, the impact of HCN2 channel blockade on ethanol-induced dopamine release in the NAc of rats was investigated through in vivo microdialysis and ECD-HPLC. The findings demonstrated that all blockers dose-dependently reduced ethanol-induced dopamine release in the NAc. In the second experiment, rats were subjected to stereotaxic guide canula implantation to lateral ventricle, after a recovery period, drugs or vehicle was administered i.c.v per five days, then, the rats were exposed to a two-bottle paradigm consumption per thirty days. The findings demonstrated that all three blockers reduced the ethanol consumption without affect mainly the total fluid intake. These results suggest that this approach has promise in mitigating rewarding effects of ethanol.

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M1 muscarinic acetylcholine receptor ligands modulate the operant oral ethanol self-administration

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Introduction. The mesocorticolimbic dopamine (DA) system plays a crucial role in mediating the addictive and reinforcing effects of ethanol (EtOH). However, other neurotransmitter systems modulate DAergic function in the nucleus accumbens (nAcc), such as acetylcholine (Ach). Ach actions are induced through binding to nicotinic and muscarinic receptors, and the M1 muscarinic acetylcholine receptor is expressed in various regions of the forebrain, including the nAcc, and could play a role in drug abuse-related behaviors. For instance, some studies have reported that the administration of an M1 acetylcholine receptor antagonist reduced the rewarding properties of cocaine and morphine. The present study aimed to assess the effects of intra-accumbal administration of the M1 muscarinic Ach receptor ligands on the operant oral self-administration of EtOH in rats. METHOD. Male Wistar rats (250-300 g) were used. Rats were water-deprived for 23.30 h and trained to lever-press for EtOH at 12% on an FR3 schedule of reinforcement until the response rate remained stable at 80%. After this behavioral training, rats received intra-accumbal injection of M1 muscarinic acetylcholine receptor agonist carbachol (1.25, 2.5 y 5.0 µg) or M1 muscarinic acetylcholine receptor antagonist pirenzepine (8.75, 17.5 y 35.0 µg) or the combination of carbachol (5.0 µg)+pirenzepine (8.75, 17.5 y 35.0 µg). RESULTS. The data showed that intra- accumbal carbachol injections increased operant oral EtOH self-administration, while pirenzepine reduced these effects. These findings suggest that M1 muscarinic acetylcholine receptor ligands modulate the operant oral EtOH self-administration in rats.

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Fenofibrate decreases ethanol-induced neuroinflammation and oxidative stress and reduces alcohol relapse in rats by a ppar-dependent mechanism

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High ethanol consumption triggers neuroinflammation, implicated in sustaining chronic alcohol use. This inflammation boosts glutamate, prompting dopamine release in reward centers, driving prolonged drinking and relapse. Fibrate drugs, activating peroxisome proliferator-activated receptor alpha (PPAR-α), are known for their antiinflammatory properties. In this context, it is very interesting to study whether they have an impact on ethanol-induced neuroinflammation, as well as on relapse. Here, we studied, in UChB drinker female rats, whether the administration of fenofibrate in the withdrawal stage after chronic ethanol consumption reduces voluntary intake when alcohol is offered again to the animals (relapse-type drinking). Furthermore, we determined if fenofibrate was able to decrease ethanol- induced neuroinflammation and oxidative stress in the brain. Animals treated with fenofibrate decreased alcohol consumption by 80% during post-abstinence relapse. Furthermore, fenofibrate decreased the expression of the proinflammatory cytokines tumor necrosis factor-alpha (TNF-α) and interleukins IL-1β and IL-6, and of an oxidative stress-induced gene (heme oxygenase-1), in the hippocampus, nucleus accumbens, and prefrontal cortex. Animals treated with fenofibrate showed an increase M2-type microglia (with anti-inflammatory proprerties) and a decrease in phagocytic microglia in the hippocampus. A PPAR-α antagonist (GW6471) abrogated the effects of fenofibrate, indicating that they are dependent on PPAR-α activation. These findings highlight the potential of fenofibrate, an FDA- approved dyslipidemia medication, as a supplementary approach to alleviating relapse severity in individuals with alcohol use disorder (AUD) during withdrawal.

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Fenofibrate administration during abstinence reduces glutamatergic tone and increase dopaminergic tone in the nucleus accumbens of rats, mediated by central pparα activationn

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Recent studies show that chronic alcohol consumption reduces glutamate transporter 1 (GLT-1) expression in astrocytes, increasing extracellular glutamate (Glu) levels and dysregulating dopaminergic tone, enhancing ethanol´s (EtOH) rewarding effects. This study aims to determine if central PPARα activation by fenofibrate normalizes GLT-1 expression and glutamatergic tone, potentially restoring dopaminergic balance in the mesolimbic pathway and reducing EtOH´s reinforcing properties.

Three experiments were conducted in UChB female rats, each undergoing the same protocol of chronic EtOH consumption for 2 months, followed by a 15-day abstinence period. During the last 5 days of abstinence, the animals were treated with fenofibrate for 1 week. In the first experiment, EtOH consumption was measured post-abstinence. In the second one, no-net-flux microdialysis in the nucleus accumbens was performed to determine extracellular Glu and dopamine levels by HPLC. In the third experiment, rats received I.C.V. treatment with a PPARα antagonist in order to differentiate central vs. peripheral effects of PPARα activation. The studies demonstrate that fenofibrate reduces voluntary consumption during relapse (ADE) by 35% and up to 70% upon continuous fenofibrate treatment. No-net-flux microdialysis in the nucleus accumbens revealed that, although there were no changes in extracellular glutamate levels, an increase in reuptake was observed. Additionally, a decrease in extracellular dopamine was observed, along with a higher reuptake rate post-treatment.

These findings provide evidence to support the use of fenofibrate in normalizing the imbalanced neurochemistry of alcohol use disorder, suggesting it as a potential therapeutic strategy for this condition.

Keywords: *Alcohol, Chronic Consumption, Fenofibrate, Glutamate, Dopamine, GLT-1, UChB rats*

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Evaluation of the effect of ALDA-1 on the activity of COX-1 and COX-2 in HEK-293 cells

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Excessive alcohol (ethanol) consumption poses a significant challenge to public health globally, leading to severe complications such as cardiovascular, kidney, and liver diseases. This metabolic process of alcohol is primarily mediated by the enzyme alcohol dehydrogenase (ADH), which converts ethanol into acetaldehyde, which is then metabolized by aldehyde dehydrogenase (ALDH2). Acetaldehyde has neurotoxic effects linked to alcohol addiction. Research in the Experimental Pharmacology lab at the University of Chile has shown that Alda-1, an activator of ALDH2, can reduce voluntary alcohol consumption in animal models by facilitating the elimination of acetaldehyde in the central nervous system. Recent studies indicate that flurbiprofen, a non-steroidal anti-inflammatory drug, also increases ALDH2 activity like Alda-1, reducing alcohol consumption in drinking rats. In this context, there has been motivation to evaluate whether Alda-1 exhibits anti- inflammatory activity similar to flurbiprofen, analyzing its effect on COX-1 and COX-2 enzymes in HEK-293 cells. Despite using HEK-293 cell cultures transfected with plasmids coding for COX-1 or COX-2, a suitable method to measure the activity of these enzymes could not be established. Therefore, a commercial kit was used, demonstrating that Alda-1 does not act as an inhibitor of COX-1 or COX-2, unlike flurbiprofen, which proved to be an effective non-selective inhibitor for both enzyme isoforms. Furthermore, molecular docking analysis revealed the differences in the interaction of Alda-1 and flurbiprofen at the active site of COX-1, explaining the divergences in their inhibitory activity.

Keywords: *Alda-1, COX-1, COX-2, Flurbiprofen and addiction*
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Effect of ALDA-1 on concurrent intake of alcohol and nicotine in rats

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This study aims to investigate the effect of Alda-1, a pharmacological activator of ALDH2, on the concurrent chronic and relapse-like consumption of alcohol and nicotine in rats. Furthermore, its effects on different cerebral biomarkers of oxidative stress were also assessed. UChB (Wistar-derived) rats were exposed to a three-bottle free choice paradigm, where they could choose between water, 30% ethanol, or 100 mg/L nicotine solutions. Animals reached a mean intake of 14.8 g/kg/day of ethanol and 3.6 mg/kg/day of nicotine. Then, Alda-1 (25 mg/kg, i.g.; n=14) or vehicle (n=15) were administered for 7 days to evaluate the effect on chronic consumption. Results showed that treatment with Alda-1 reversibly reduced by approximately 80% the consumption of both ethanol and nicotine solutions compared to vehicle. Afterward, animals were deprived of ethanol and nicotine consumption for 14 days and then treated with Alda-1 or vehicle for the last seven days of deprivation. At this point, the two groups of animals were divided into abstinence groups and reaccess groups. Abstinence groups went through microdialysis to determine glutamate extracellular levels in the Nucleus Accumbens, obtaining no significant differences between Alda-1 or vehicle administration. While reaccess groups continued under Alda-1/vehicle treatment for 7 days more, where they were able to drink ethanol and nicotine freely. Results showed no effect of Alda-1 on relapse-like intake of nicotine and ethanol solutions. Brain levels of 4-HNE, MDA, and GSSH/GSH were assessed for all groups, and no differences were observed for any treatment condition.

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Aging is associated to reduced glycine receptor in nucleus accumbens and reduced ethanol preference in mice

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The nucleus accumbens (nAc), a central region of the mesolimbic system, has been linked to addiction and shows alterations with age. This study aimed to investigate the impact of aging on the expression of ethanol-sensitive glycine receptors (GlyRs) in medial spiny neurons (MSNs) of the nAc and their influence on ethanol-related behaviors.

We evaluated GlyRs expression and neuronal activity in the nAc of 2-, 6-, and 12- month-old C57BL/6 and BAC Drd1a-tdTomato mice. Intracellular Ca^{2+} dynamics were quantified in response to strychnine (STN) and ethanol (EtOH) exposure. The findings revealed a significant age-related decrease in Ca^{2+} transients, with neuronal activation decreasing from 276% at 2 months to 112% at 12 months (<0.05) when slices were treated with STN. EtOH administration significantly reduced Ca^{2+} transients at two months compared to 6 and 12 months (<0.0029). Immunohistochemistry and RT-qPCR results indicated a reduction in α1-subunit expression in MSN-D1+ at 6 and 12 months (<0.05). Results from behavioral assays indicated a loss of conditioning to ethanol in 6-month-old mice, which was reversed by overexpression of the α1 subunit (<0.05).

The study concludes that aging significantly reduces GlyR expression and activation in the nAc, particularly the α1 subunit in MSN-D1+. This reduction may contribute to dopaminergic imbalances and behavioral changes, including reduced conditioning to EtOH. These findings provide insight into EtOH-related behavioral changes during aging and may also explain the generalized decrease in responsiveness to rewarding stimuli in older individuals.

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Reward memory: the role of the periaqueductal gray

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The reward system plays a fundamental role in motivation, learning, and reward-seeking behavior. Dysfunction of this system is associated with neuropsychiatric disorders such as substance use disorder. Although the periaqueductal gray matter (PAG) is not traditionally considered part of the reward system, recent evidence suggests its involvement in modulating motivation and reward-seeking behavior. To address this proposal, neuronal activation in the l/vlPAG was characterized during learning and reward memory and the activation pattern of this region was investigated together with the monitoring of the animal´s behavior. Moreover, it is hypothesized that its activation goes beyond the role of opioid receptors. To that, we too evaluate cocaine's neuronal activation in the l/vlPAG during learning and reward memory. Our results showed an increase in CPP scores of cocaine-conditioned and ethanol-conditioned mice; however, there was no significant effect observed for saline-conditioned mice ($n=10$, $P < 0.01$, $F = 10.003$). We explored the activation changes of l/vlPAG by the c-Fos immunofluorescence staining. Activated neurons in this region were significantly increased compared with the control group ($n = 6$, $P < 0.05$, $F = 49.61713$).

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Changes in properties of glycine receptors in aged accumbal neurons alter ethanol consumption in mice

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Glycine receptors (GlyR) are inhibitory ligand-gated ion channels present in the nucleus Accumbens (nAc), and are important for the regulation of nAc excitability and ethanol consumption. In this study, we examined the expression and properties of GlyRs in the nAc of young, adult and aged C57/BL6 mice (2, 6 and 12 months old), and ethanol consumption as well.

RT-qPCR analysis showed a reduction of the α2, α3 and β subunits of the receptor, however, western blot analysis showed that protein expression is not significantly altered with age. Despite this, accumbal neurons of older mice had a lower percentage of neurons presenting glycinergic synaptic events (43% at 12 months compared to 64 and 54% at 2 and 6 months respectively). The glycine concentration-response curve at 12 months was displaced to the right with an EC 50 of 91 µM compared to 52 µM at 6 and 42 at 2 months. The current density of glycine and ethanol sensitivity of GlyRs in these neurons was also reduced. Ethanol potentiation was around 78%, 36%, and 26% for 2, 6, and 12 months, respectively (with 100 mM). In terms of ethanol consumption, older mice, starting at 6 months, drink less than young animals and have lower blood ethanol concentration.

These findings are relevant considering the role of GlyRs in nAc regulation. The lower activation of GlyRs in the nAc of mice at different ages suggests a change in subunit expression with reduced ethanol sensitivity. This seems to have an impact on mice behavior towards ethanol.