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Cross-sectional and longitudinal evidences of changes in alcohol consumption patterns after COVID-19 pandemic in Spain: the role of psychological distress and sociodemographic profile

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ABSTRACT

The COVID-19 pandemic brought significant changes in many different aspects, among them, alcohol consumption patterns, and mental health. Aims: i) to examine the changes in alcohol use (quantity, frequency, binge drinking) during the pandemic among Spanish adults, ii) to examine the impact of psychological distress (depressive/anxiety symptoms, negative affect), and sociodemographic characteristics (gender, age, living/college status) on changes in alcohol use patterns. To achieve these aims, two studies are presented. In study 1, a cross-sectional online sample of 1417 adults (M_{age}=30.7, *SD*=8.6), recruited during the Spanish lockdown, were queried about their pre-post COVID-19 self-perceived changes in alcohol consumption. In study 2, 305 community young adults (M_{age}=21.3, *SD*=2.2) completed two surveys (before the COVID-19 outbreak, and one year after). In both studies, alcohol consumption decreased after the COVID-19 outbreak. In study 1, age, living alone (in opposition to living with others), and negative affect were positively associated with self-perceived increases in drinking frequency and binge drinking. Also, living status moderated the positive relationship between negative affect and drinking frequency. In Study 2, participants with more depressive symptoms before COVID-19 were less likely to reduce their alcohol use (frequency and quantity) after COVID-19 outbreak. Moderation analysis showed that drinking frequency decreased among college students, but not in non-college participants. Conclusions: Consistently with previous studies, alcohol use decreased after COVID-19 outbreak, and psychological distress and sociodemographic characteristics played a key role in alcohol consumption changes. These findings may be useful to inform interventions aimed at reducing alcohol-related harms during public health crises.

Keywords: Alcohol, COVID-19, anxiety, depression, distress, sociodemographic profile

Personality Pathways to Alcohol Use: The Roles of Impulsivity and Compulsivity

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ABSTRACT

Research on the etiology of alcohol use disorder (AUD) has identified different non-mutually exclusive pathways that can lead to alcohol use and alcohol-related problems during adolescence. Some of these pathways are characterized by the presence of personality traits that constitute risk factors for AUD.

The most investigated personality traits linked to alcohol use have been impulsivity and negative affect. However, in recent years, neurobiological research has emphasized compulsivity as a more proximal risk factor for AUD. Although new measures that conceptualize compulsivity as a personality trait have been developed, the role of compulsivity within the personality pathways to substance use is understudied. Here, results from a longitudinal study using an adolescent cohort (N = 851, mean age = 13.2 at baseline) are presented, showing 1) the role of impulsivity in alcohol use initiation; 2) bidirectional associations of impulsivity and negative use with progression to regular alcohol use; 3) the association of compulsivity traits with AUD symptomatology; and 4) the mediating role of compulsivity in the association of impulsivity and negative affect with alcohol-related problems. Taken together, these findings suggest that compulsivity might constitute a crucial link in the personality pathways to AUD, that should be targeted in assessment and preventive interventions with adolescents.

Keywords: impulsivity, compulsivity, negative affect, adolescents

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

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ABSTRACT

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

Funding: This work was supported by Anillo ANID ACT210012

Keywords: neuroinflammation, glutamate transporter, fibrates

Adaptation and implementation of the Icelandic model for the prevention of substance abuse in communes of the Metropolitan region of Chile

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ABSTRACT

Adolescent alcohol and other drugs use is one of the biggest public health problem worldwide. Evidence-based preventive strategies are very scarce in Chile. The Icelandic Prevention Model (IPM) has shown positive results in that country. The IPM is a community prevention model, focused on modifying the environment, driven by local information in a collaborative process between decision makers, community workers and academics. In 2018, the adaptation and implementation work began with a first local school's survey in collaboration with 6 districts of Santiago and the Universities of Reykjavik and Chile. Although the pandemic interferes with the interpretation of the results, a decrease in substance use in adolescents is observed in the 2020 and 2022. Through qualitative methods, we observe that IPM is accepted mainly for generating consensus regarding the prevention approach. The main barriers are cultural and socioeconomic factors. More research is required regarding the effectiveness and mechanisms of IPM.

Keywords: prevention, substance use, adolescent, implementation

Neuroinflammation in a rat model of prenatal alcohol exposure

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ABSTRACT

Maternal exposure to a single high dose of ethanol during the last week of pregnancy caused astrocyte reactivity and exacerbated endoplasmic reticulum stress in the hippocampus of newborn rat pups, suggesting significant damage of the central nervous system. To know whether this unique maternal alcohol exposure elicited an inflammatory state in the offspring, we investigated the levels of Iba1 and of inducible nitric oxidase synthase (iNOS) as well as those of the pro-inflammatory cytokines tumor necrosis factor alpha (TNFα); interleukin (IL) 1 beta (IL-1β) and IL-6, and those of the inflammatory effectors, matrix metalloproteinase (MMP) -2 and -9 that were significantly augmented in adult alcoholics. Preliminary results showed increased hippocampal Iba1 immunoreactivity, no changes in iNOS expression, and marginally significant increases in IL-1β and unclear results in MMPs. New experiments are necessary to propose a clear dependency between exacerbated glial reactivity and neuroinflammation with a single maternal alcohol exposure.

Keywords: prenatal alcohol exposure, glial reactivity, pro-inflammatory cytokines

Testing the stability of alcohol expectancies and drinking contexts as predictors of changes in alcohol consumption among young university students before and during the Argentinean quarantine due to the COVID-19 pandemic: A one-year follow-up study.

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ABSTRACT

Aims: a) To evaluate within-person changes in alcohol consumption in Argentinean young university students, from August 2019 to one-year follow up during the COVID-19 restrictive quarantine, considering alcohol expectancies, drinking contexts, and main socio-demographic variables as predictors; b) to assess the stability of these predictors' effects on the alcohol consumption through dependent and independent measures. **Methods:** This study included one longitudinal (N = 300, with T1 in August 2019 and T2 in August 2020) and one cross-sectional (N = 165, collected parallelly in August 2020) sample. Multilevel analysis and multiple regressions were calculated on the longitudinal and cross-sectional sample, respectively. **Results:** Alcohol consumption was higher during the COVID-19 restrictive quarantine compared to one-year before. In the longitudinal sample, predictors having stable increasing effects on alcohol consumption were social facilitation, stress control, and parental control, while age of onset was the only one having a stable inverse effect on consumption. In the cross-sectional sample, positive alcohol expectancies, stress control, and parental control were related to higher alcohol consumption during quarantine, while having high socioeconomic status was related to lesser alcohol consumption as compared to medium socioeconomic status. **Conclusions:** Stress control and parental control contexts were stable predictors increasing alcohol consumption before and during COVID-19 quarantine. The finding that the variable parental control context has an increasing effect on alcohol consumption was unexpected. Training in strategies to cope with stress and parental education on the deleterious alcohol-related effects could help reduce alcohol consumption in university students during both quarantine and non-quarantine situations.

Keywords: alcohol drinking, alcohol drinking in college, COVID-19, longitudinal studies, expectations, quarantine; developing countries

Targeting HCN2 ion channels as a therapeutic strategy for alcohol use disorders

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ABSTRACT

A recognized target for ethanol-addictive effects is the dopaminergic circuitry of the ventral tegmental area (VTA), which is part of the dopamine mesocorticolimbic system. Ethanol can stimulate VTA dopamine neurons by increasing their activity, thus releasing dopamine in the nucleus accumbens. The excitability of VTA dopamine neurons is largely controlled 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 these activating actions of ethanol can be inhibited by HCN blockers. The overexpression of the HCN2 isoform in the mesolimbic system have been associated with increased rewarding and stimulant effects of ethanol in rats, while the gene knockdown of HCN2 channels in the VTA has been associated with a reduction of ethanol consumption by the animals. The development of drugs selective for neuronal HCN2 channels would provide new therapeutic tools for alcohol addiction.

Keywords: Ethanol, HCN2 channels, blockers, rats

An interpretive approach about alcohol consumption during pregnancy in Brazil

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ABSTRACT

The purpose of this qualitative research was to uncover elements to improve understanding of alcohol consumption among pregnant women in Brazil. Fourteen women who reported drinking alcohol while pregnant were interviewed. Alcohol consumption during pregnancy seemed to be linked with three groups of interconnected issues: subjective and individual issues (such as expectations, motivations, and women's difficulty identifying their own consumption as risky); sociocultural and environmental issues (such as alcohol's cultural value, easy access, and influence from relatives, friends, and partners); misinformation and a lack of technical addressing of the subject during prenatal care. To reduce alcohol intake among Brazilian women, it appears that both collective and individual health education efforts are required. Media campaigns with detailed information on the damaging effects of alcohol, accompanied by individualized actions with a systematic approach to this issue during prenatal care, could allow for earlier and more suitable diagnosis and intervention of at-risk women.

Keywords: pregnancy, alcohol consumption, motivation, health promotion, qualitative research, Brazil

Sex differences in startle reactivity and endocannabinoids expression in the amygdala after exposure to predator odor stress

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ABSTRACT

Alcohol misuse and post-traumatic stress disorder (PTSD) are highly comorbid, and treatment outcomes are worse in individuals with both conditions. Although more men reported experiencing traumatic events than women, lifetime prevalence of PTSD is twice as high in females. Despite this clear sex bias on trauma-related response, preclinical studies are overwhelmingly performed with male animals. In this symposium, I will discuss how voluntary alcohol drinking affects avoidance behavior, acoustic startle response and endocannabinoid levels in the amygdala of male and female rats exposed to predator odor stress. I will address sex differences in behavioral and endocrine responses to stress and the importance of considering sex as a biological variable.

Keywords: alcohol consumption, post-traumatic stress disorder, acoustic startle response, endocannabinoids

Therapeutic effects of ayahuasca on alcohol use disorder: pre-clinical evidence

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ABSTRACT

Ayahuasca, a hallucinogenic beverage used in traditional Amazonian communities for ritualistic and curative purposes, has been proposed as a potential treatment for alcohol use disorder. Clinical studies show that ritualistic use of ayahuasca is associated with lower alcohol use and related problems compared to the general population. Importantly, by removing the social and ritualistic aspect of ayahuasca use in humans, pre-clinical studies have contributed to elucidate whether ayahuasca has pharmacological effects that contribute to its therapeutic utility. This talk will cover the most recent

studies from our laboratory investigating the effects of ayahuasca on abuse-related behavioral effects of alcohol in mice. Specifically, we have investigated the effects of ayahuasca on alcohol-induced behavioral sensitization, conditioned place preference and self-administration (two-bottle choice) in mice. Overall, our findings show that treatment with ayahuasca blocks the development and expression of the abuse-related behavioral effects of alcohol. Some specific experimental conditions, such as the treatment environment and dose, can influence the emergence of the therapeutic effects of ayahuasca in pre-clinical models. Our studies also suggest that serotonergic mechanisms seem to play a role in the effects of ayahuasca on alcohol abuse. These findings corroborate clinical studies suggesting that ayahuasca may have therapeutic effects on alcohol abuse.

Keywords: ayahuasca, ethanol, mice, conditioned place preference, behavioral sensitization, self-administration

Binge drink effects on the adolescent brain: consequences for adulthood

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ABSTRACT

Alcohol (ethanol) experimentation usually starts during adolescence, the final stage of neurodevelopment. It is becoming very common among young people to consume many doses of the drug in a short period of time, which leads to high levels of alcoholic intoxication. This type of behavior during adolescence is a risk factor for poor decision-making, maladaptive risk-taking and anxiety behavior, which are influenced by inhibitory control processes. Several brain regions including the Basal Ganglia, in particular some neuronal pathways generated in the external Globus Pallidus, participate in the inhibitory control behaviors. In previous studies, we and others have shown changes in the connectivity of the Globus Pallidus after ethanol intoxication. Indeed, in rodents, we found a specific effect of ethanol on decreasing the firing rate of two neuronal subtypes, the arkypallidal and the low-frequency prototypical neurons, of the external part of the Globus Pallidus in adolescent mice. More recent, we have been observing that the high levels of intoxication during adolescence can lead to changes in risk-taking, anxiety like-behavior and ethanol voluntary drinking during adulthood in a sex-dependent manner. Previously intoxicated animals made less risk-assessment behaviors than naive mice, which indicated higher anxiety. Females mice intoxicated with ethanol during adolescence show anxiolytic-like effects to ethanol re-exposure. Intoxicated males, otherwise, showed high levels of basal anxiety-like behavior, which was reversed by an acute exposure to ethanol during adulthood. In addition, adolescent intoxicated females consumed more ethanol in adulthood than control females doing more bouts than controls. Male intoxicated mice did not consume more ethanol, but they decreased the time to do the first bout after repeated drinking tests. Heavy alcohol intoxication during adolescence alters anxiety and risk-assessment behaviors as well as drinking in adulthood, with specific effects for each sex.

Keywords: binge drinking, adolescent, long-term effects, animal models

Ethanol vs social rewarding: what is the choice for mice under environmental enrichment?

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ABSTRACT

Social interaction plays an important role in drug addiction outcome. We have used the model of environmental enrichment (EE) to evaluate changes in rewarding effects of alcohol in animals, since one of the pillars of EE is to increase social interaction. We previously reported an increase in the levels of the prosocial neuropeptide, oxytocin (OT), in the hypothalamus of enriched mice, as well as enhanced rewarding effects of ethanol. The present study examined the effects of EE on a) conditioned place preference (CPP) to ethanol vs social stimulus, b) dominance-related behavior, and c) motivation to appetitive reward conditions. We also evaluated the effects of EE on phospholipase C (PLC) activity in striatal membranes following OT receptor (OTR) activation. We assessed D1 and D2 receptors (DR) expression in the nucleus accumbens (NAc) given their role in motivation towards social and drug rewarding behaviors. Our findings revealed that EE animals exhibited a higher preference for etanol even in the presence of a social stimulus; higher social dominance, and lower motivation for appetitive taste stimuli. PLC activity was significantly lower in the striatum of EE animals. Western blot analyses of DR revealed a significant increase in D1R but not D2R in the NAc of EE mice over controls, which was blocked by the administration of the OTR antagonist (L-368-889). Our results suggest that the changes in OT and DA signaling could be partially responsible for higher alcohol preference by EE animals and suggest that social reward may not be sufficient to protect against alcohol reward.

Keywords: environmental enrichment, ethanol, social reward, conditioned place preference, oxytocin

Sex differences in negative affect, pain, and extended amygdala signaling following adolescent alcohol exposure

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ABSTRACT

Adolescent alcohol use is one of the strongest predictors for development of an alcohol use disorder, yet many of the long-term consequences are still unknown. Hyperkatifeia is a term coined to describe the combined enhancement of negative emotional states and hyperalgesia during alcohol withdrawal leading to relapse and continued alcohol use. Negative affect and pain are more prevalent in women than men and may disproportionately drive drinking and relapse. However, the development and underlying mechanisms driving the sexual disparity in risk factors are unknown. A region of interest to investigate these mechanisms is the extended amygdala (the bed nucleus of the stria terminalis, BNST, and central nucleus of the amygdala, CeA). These regions are known to integrate alcohol- and stress-related information to regulate “emotional” and pain-related behaviors. We use an adolescent intermittent ethanol vapor exposure paradigm (AIE) in male and female rodents to explore long-term changes in negative affect, hyperalgesia, and associated changes in extended amygdala function. To assess negative affect-like behavior, AIE mice are tested as adults in the novelty-induced hypophagia (NIH) task following restraint stress and low-intensity contextual fear conditioning. Female mice with AIE history show increased negative affect in the NIH task in response to stress, but AIE-treated males do not. Male but not female mice with AIE history show increased contextual fear learning. As $mGlu_5$ receptors are important for alcohol-induced negative affect, we site-specifically knocked down mGlu5 receptors in the dlBNST and find enhanced NIH

latency in females, with no effect on male NIH latency or fear learning in either sex. BNST $mGlu_{1/5}$-mediated long-term depression is also altered in female mice with an AIE/stress history but not male mice. Other experiments tested thermal (Hargreaves) and mechanical (Von Frey) hyperalgesia during and following AIE in male and female rats. These studies find rapid and long-lasting (6 weeks post exposure) thermal and mechanical hyperalgesia in male but not female rats. CeA cells that project to the ventrolateral periaqueductal gray (vlPAG) have reduced synaptic strength following AIE in male but not female rats. These results indicate that adolescent alcohol exposure produces long-lasting sex-dependent changes in negative affect and pain associated with extended amygdala dysregulation.

Keywords: adolescence, ethanol, rats

Secretome derived from mesenchymal stem cells as a new biodrug for the treatment of alcohol use disorders: Toward the identification of therapeutic molecules

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ABSTRACT

Chronic alcohol consumption leads to neuroinflammation and oxidative stress, which inhibit the astrocyte Na-glutamate-transporter (GLT-1), proposed to perpetuate alcohol intake. The secretome derived from mesenchymal stem cells (MSCs) contains potent anti-inflammatory and antioxidant molecules. We showed that intranasal administration of MSC-derived secretome in a rat model of chronic ethanol intake: (a) inhibited ethanol intake and relapse; (b) inhibited alcohol-induced neuroinflammation and oxidative stress and (c) increased brain GLT-1 levels. Knockdown of GLT-1 by administration of an antisense oligonucleotide fully abolished the inhibitory effect of MSC-derived secretome on ethanol intake, suggesting that GLT-1 mediates the MSCs therapeutic effects. Using artificial intelligence, we conducted multiple protein-protein interaction in the GLT-1 network (PPI-analysis), allowing the identification of proteins in the MSCs secretome that are strongly represented in the GLT-1-PPIs network. Overall, studies indicate that administration of MSC-derived secretome or specific molecules contained in it afford translational opportunities for the treatment of alcohol-use disorders.

Keywords: GLT-1; biodrug; stem cells; polyaddiction.

Gut microbiota markedly influences ethanol intake and relapse. A role for probiotics in reducing alcohol intake

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ABSTRACT

Gut microbiota can influence the rewarding effects of alcohol via: (i) bacterial products released into the systemic circulation and (ii) activation of the gut afferent vagus nerve. Present studies investigated the role of gut microbiota on ethanol intake and relapse in a rat model (UChB) bred for its high voluntary ethanol preference. Oral administration of

two non-absorbable antibiotics reduced bacterial composition and reduced ethanol intake by 65% ($p<0.001$), while the oral administration of Lactobacillus-GG to naïve animals increased the systemic level of FGF21 (an activator of dopamine transporter synthesis) and reduced alcohol intake by 35% ($p<0.001$). Rodents electrically self-stimulate the vagus nerve indicating a rewarding action, and effect shared by alcohol-released bacterial products. Vagotomy inhibited ethanol intake by 80% ($p<0.001$). Consistent with these findings, Lactobacillus administration and vagotomy markedly inhibited the binge-relapse (ADE) following chronic intake and deprivation, also potentiating the inhibition of ethanol intake of anti-inflammatory and antioxidant drugs.

Keywords: Gut microbiota; Lactobacillus, antibiotics; alcohol deprivation effect (ADE); vagus nerve.

What we have learned from the use of ayahuasca in substance-related effects?

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ABSTRACT

Ayahuasca (AYA), a beverage containing N,N-dimethyltryptamine (DMT), was originally used during indigenous Amazon rituals. Clinical studies have shown the beneficial effects of AYA in the treatment of several mental illness as well as substance-related disorders. We evaluated AYA effects on ethanol and cocaine-induced expression of locomotor sensitization, as well as on cocaine-induced expression of conditioned place preference (CPP). Swiss mice received 2.2g/kg ethanol or saline i.p. every other day for 9 days, and locomotor activity was evaluated 10min after each injection. Then, animals were treated daily with AYA (corresponding to DMT 1.76mg/kg) or water by oral gavage for 8 days. AYA attenuated the expression of locomotor sensitization. However, the same dose of AYA did not block the expression of locomotor sensitization of C57Bl/6 mice treated with cocaine (10mg/kg) i.p. in a similar protocol. A corresponding dose of DMT 15mg/kg of AYA was needed to attenuate the expression of locomotor sensitization. On a CPP protocol we evaluated: (i) Effects of AYA on CPP (2.5; 7.5; 12.5 and 15mg DMT/kg v.o.); (ii) Competition between cocaine and AYA-induced CPP (odd days: cocaine 10mg/kg; even days: AYA - 15mg of DMT/kg). (iii) Acute administration of AYA on cocaine CPP expression (mice were submitted to four cocaine conditioning sessions; on the test day, they received water or AYA (12.5 or 15mg of DMT/kg). Results: (i) only 15mg DMT induced CPP. (ii) Cocaine-induced CPP prevails upon AYA -CPP. (iii) Both doses prevented the expression of cocaine-induced CPP. Although AYA showed positive results in ethanol and cocaine behavioral models, the need of high dose of DMT was needed with cocaine.

Keywords: ayahuasca, ethanol locomotor sensitization, cocaine locomotor sensitization, conditioning place preference, mice

Parenting experiences: impact on behavior and response to alcohol

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ABSTRACT

Parental behavior during early development has a strong influence on the emotional and social development of infants. Literature on parenting, human or animal, has primarily focused on the interactions between mothers and offspring, with little

research directed at understanding on what paternal behavior could add to infant social attachment. Strong ties or social attachment as pair bond formation in adult rodents has protective effects on neurodevelopment and against drug effects. In this sense, rearing conditions during early ontogeny may have differential effects infant development and drug experience. The present project analyzed if different parenting conditions (ie., single-mother -SM- or biparental care -BP-), in a non-monogamous mice strain (C57BL/6), may have a differential impact on the parenting during lactation, adolescent behavior and response to ethanol of the offspring. Or results evidenced that these two rearing conditions implied differential parental behavior during lactation period. In fact, SM condition induced an anxiety-like behavior and major alcohol consumption in adolescent offspring, compared to BP-animals. Moreover, these adolescents were more sensitive to ethanol-induce anxiolysis, and less sensitive to ethanol-induced motor activation. A neurobiological approach indicated that SM derived infants had great neural activation in brain areas related to anxiety behaviors as the amygdaloid circuit and this effect was increased by ethanol treatment. These results highlight the importance of parenting during a critical period of early development and the long-lasting effects of social experience.

Keywords: parental behavior, adolescence, anxiety, ethanol response

Can EE restore the effects of prenatal ethanol exposure?

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ABSTRACT

Prenatal ethanol exposure (PEE) is associated with several deleterious effects, including alterations in gene expression of key systems responsible for processing of ethanol's motivational effects. We observed that PEE upregulated κ opioid receptors (KOR) mRNA levels in the prefrontal cortex, and prodynorphin (PDYN) and KOR mRNA levels in the ventral tegmental area (VTA), in Wistar rats. Treatments to prevent or reduce the consequences of PEE are scarce. Environmental enrichment (EE) is a non-pharmacological intervention, valuable to reduce the effects of environmental toxins and some psychoactive drugs. The studies that have analyzed the modulation of ethanol's effects by EE have provided, however, mixed results. Studies conducted in several labs have revealed that EE, applied for a short time during adolescence, results in enhanced ethanol intake or reinforcement, for instance measured via conditioned place preference. After finding these outcomes, we applied a protracted EE protocol, from gestational day 20 to postnatal day 26, to rats that had been exposed (or not, control group) to PEE (2.0 g/kg ethanol, gestational days 17-20). EE ameliorated or normalized a PEE-induced upregulation of KOR gene expression in amygdala, a PEE-induced exacerbation of PDYN gene expression in VTA, and alterations in BDNF mRNA levels in VTA and Nucleus accumbens. EE also normalized PEE-induced lower DNA methylation at the PDYN gene promoter. These results suggest that EE, when applied in a relatively lengthy fashion, can help reverse PEE-induced alterations in gene expression. Future studies should analyze if this protocol can also reduce other effects of PEE.

Keywords: prenatal ethanol exposure, rat, environmental enrichment, gene expression

GABAERGIC MECHANISMS IN THE REINFORCING EFFECTS OF ETHANOL

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ABSTRACT

Ethanol's ability to potentiate the activity of gamma-aminobutyric acid (GABA) at GABA-A receptors has been implicated as a key mechanism underlying the reinforcing effects of ethanol in both humans and laboratory animals, making this system an attractive candidate for the development of therapeutics. GABA-A receptors are heteromeric complexes comprised of multiple subunits, with the alpha subunit often determining the pharmacology associated with the receptor. This complex molecular biology of GABA-A receptors raises the possibility that subtype-selective agents can be developed with therapeutic specificity against the abuse-related effects of ethanol. Using ligands selective for different GABA-A receptor subtypes as pharmacological tools, we determined the extent to which selective positive, neutral, and negative modulators selectively altered ethanol self-administration in rhesus monkeys. In ethanol drinking monkeys, concentrations of 1-6% (w/v) ethanol maintained self-administration above water levels, engendered pharmacologically-relevant blood ethanol levels ranging from 90-160 mg/dl, and produced changes in behavior typical of ethanol intoxication. In sucrose drinking monkeys, concentrations of 0.3-3% (w/v) sucrose maintained reliable self-administration. In pretreatment studies, positive modulators of alpha5- and alpha2/3-containing GABA-A receptors enhanced ethanol, but not sucrose, self-administration and negative modulators of alpha5-containing GABA-A receptors attenuated ethanol, but not sucrose, self-administration. In contrast, ligands selective for alpha1-containing GABA-A receptors failed to alter ethanol self-administration, up to doses that produced other behavioral effects (e.g., sedative-motor effects). These results suggest that alpha5- and alpha2/3 GABA-A receptor subtypes play key roles in ethanol's reinforcing effects and that targeting these subtypes may offer novel avenues for therapeutic development.

Keywords: alcohol self-administration, GABA, pharmacotherapy, rhesus monkeys

Programación Fetal Etílica: Mecanismos que Regulan la Subsiguiente Afinidad hacia la Droga y la Reactividad Respiratoria Frente a la Misma

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RESUMEN

La expresión Programación Fetal Etílica alude a procesos de aprendizaje no asociativos y asociativos que se derivan de capacidades fetales reclutadas por la exposición prenatal al alcohol. La mera exposición hacia componentes sensoriales de la droga, genera un proceso de familiarización olfato-gustativa que facilita el subsiguiente reconocimiento y preferencia hacia dichos componentes sensoriales. Las claves sensoriales de la droga, presentes en el líquido amniótico, guardan contingencia temporal con la acumulación etílica a nivel central. La presencia cerebral del psicotrópico actúa en calidad de reforzador positivo. Estas propiedades reforzantes están íntimamente ligadas a la producción central de acetaldehído producido por el sistema enzimático de catalasas. El feto adquiere respuestas condicionadas hacia el etanol debido a la mencionada contingencia entre la percepción sensorial de la droga y los efectos incondicionales apetitivos de la droga y/o de su principal metabolito, el acetaldehído. En forma concomitante surgen otras respuestas condicionadas que competen a procesos de orden respiratorios. El etanol a nivel incondicional deprime las respuestas respiratorias del feto y el neonato, fenómeno que también se asocia con la percepción de elementos olfatorios y gustativos de la droga. Tanto a nivel

preclínico como clínico, los estudios demuestran que la re-exposición postnatal a claves sensoriales etílicas reclutan en forma co-existente respuestas indicativas de preferencia hacia los efectos del psicofármaco como significativos procesos de depresión respiratoria. En conjunto, los resultados aquí expuestos implican la necesidad de extender el diagnóstico del Espectro de Desordenes Fetales del Alcohol a mecanismos funcionales que ejerce la droga a nivel prenatal.

Keywords: feto, programación, alcohol, función respiratoria

Alcohol consumption during COVID-19 among university students and staff in Chile: results from a longitudinal study

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ABSTRACT

The study aim was to examine changes in alcohol use throughout the COVID-19 pandemic and whether these changes differ by gender and age. Longitudinal data were collected using monthly online surveys from July 2020 to April 2021. A non-probabilistic sample of 1039 university students and staff, 69% women, completed questionnaires about past-week alcohol consumption and past-month binge drinking before and during the COVID-19 pandemic, motives of drinking, and socio-demographics. Multilevel modelling was carried out. On average, participants decreased their quantity of drinks consumed per week and were less likely to engage in binge drinking compared to the pre-pandemic period. Age-stratified analysis showed that younger participants reduced the quantity of drinks consumed per week whereas older participants maintained their pre-pandemic consumption levels. These findings contribute to understand changes in alcohol consumption during the COVID-19 pandemic and to identify and develop preventive interventions for the groups at higher risk of increasing consumption.

Keywords: Binge drinking, drinking motives, longitudinal study, multilevel modelling