general innate dysregulation of the brain stress system common to msP rats that are not directly related to the polymorphisms. This study was supported by NIH/NIAAA AA017447 (MR and RC).

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Mathematical modeling of ethanol effects on the HPA axis dynamics

Željko Čupić[1], Ljiljana Kolar-Anić[1,2], Lars Terenius[3], Vladana Vukojević[3]
[1]Institute of Chemistry, Technology and Metallurgy, University of Belgrade, Department of Catalysis and Chemical Engineering, Njegoševa 12, 11000 Belgrade, Serbia; [2]Faculty of Physical Chemistry, University of Belgrade, Studentski trg 12-16, 11000 Belgrade, Serbia; [3]Center for Molecular Medicine, Department of Clinical Neuroscience, Karolinska Institutet, CMM L8:01, 17176 Stockholm, Sweden

Alcoholism and stress are mutually related and difficult to disentangle. Numerous studies show that ***a)*** ethanol impinges on the hypothalamic-pituitary-adrenal (HPA) axis dynamics, altering individual response to stress, and ***b)*** that individuals under stress are more prone to drinking. Molecular mechanisms underlying the relationship between stress and alcohol consumption are not well understood and difficult to characterize experimentally due to the intricate nature of the problem. We use here mathematical modeling and numerical simulations to emulate ethanol effects on the HPA axis dynamics and study mechanisms through which these interactions are integrated to yield an altered response to stress. We present a low-dimensional mathematical model in which the complex regulation of HPA axis activity arises from the intrinsic nonlinearity of underlying biochemical interactions and the entanglement of investigated species via feedback mechanisms, rather than from any stochastic or noisy input from the surroundings. Modeling shows that the underlying non-linearity enables the HPA axis to quickly adjust its dynamics in response to perturbations with ethanol, and promptly restores its balance thereafter. In addition, modeling shows that chronic exposure to ethanol changes the dynamic regulation of HPA axis activity, leading to reduced and eventually loss of adaptive potential. Mathematical modeling and numerical simulations may critically contribute to the elucidation of dynamic mechanisms that regulate the function of the HPA axis at the organism level. These integrative methods enable us to mimic *in silico* the effects of acute and chronic exposure to ethanol, and investigate the impact of ethanol on the HPA axis dynamics and the response to stress.

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Heavy prenatal alcohol exposure differentially impacts the relationship between pituitary volume and behavior in male and female adolescents

Eileen M. Moore, Monica Manibusan, M. Alejandra Infante, Robyn Migliorini, Sarah N. Mattson, Edward P. Riley
Center for Behavioral Teratology, San Diego State University, San Diego, CA 92120, USA

Rodent studies demonstrate that prenatal alcohol exposure produces hypothalamic-pituitary-adrenal (HPA) axis dysregulation with sex-dependent effects on behavior. Pituitary volume may be a relatively stable and state-independent index of HPA axis function in humans. To determine if prenatal alcohol exposure produces measureable changes in pituitary volume that relate with problem behavior in human adolescents, we manually traced the pituitary in T1-weighted structural magnetic resonance images (MRI). Pituitary volumes were calculated for male and female adolescents with and without prenatal alcohol exposure and were correlated with primary caregiver ratings of behavior on the Child Behavior Checklist (CBCL). Control female adolescents presented with significantly greater pituitary volume compared to males, however this sex-effect was absent in adolescents with histories of prenatal alcohol exposure. In prenatal alcohol exposed males, scores on the CBCL aggressive behavior scale were negatively associated with pituitary volume. The lack of a sex difference in pituitary volumes between the alcohol-exposed groups suggests such exposure may interfere with adolescent typical sexual dimorphism of the pituitary. In prenatal alcohol exposed males pituitary volume may reflect cortisol levels, which have previously been reported to be negatively associated with aggressive behavior in clinical populations. These findings suggest the endocrine system is impacted by prenatal alcohol exposure, which may have implications for stress reactivity in this population. This work was supported by NIAAA grants R01 AA010417, R01 AA019605, U24 AA014811, U01 AA014834, and T32 AA013525.

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Alcohol-Responsive Synaptic MicroRNAs Coordinately Regulate MRNAs Following Chronic Alcohol Consumption

Dana Most, Yuri Blednov, R. Adron Harris and R. Dayne Mayfield
Waggoner Center for Alcohol and Addiction Research, UT Austin, Austin, TX 78712, USA

Local translation of mRNAs in synaptic compartments of the cell plays a major role in synaptic structure and function. Chronic alcohol use causes persistent changes in synaptic mRNA expression that might be regulated by microRNAs in the synapse. To determine the microRNAs that may regulate synaptic alcohol-induced mRNA adaptations, we profiled the transcriptome of synaptoneurosomes from the amygdala of mice undergoing a chronic voluntary alcohol consumption paradigm. We found 67 mature mouse microRNAs and 1,531 mRNAs differentially-expressed between the alcohol-drinking mice and the controls. 38 premature microRNAs were found differentially-expressed, 11 of which correspond to 12 alcohol-responsive mature microRNAs. To predict mRNA-microRNA interactions we used two approaches: (1) mRNA-microRNA co-expression using weighted gene co-expression network analysis (WGCNA) and (2) mRNA-microRNA target prediction using mirSVR scores in miRanda. WGCNA highlighted many co-expressed mRNAs and microRNAs that have high correlations with alcohol consumption. The biological pathways associated with the co-expressed mRNAs include long-term potentiation and depression, glutamate signaling, neuroimmune processes, RNA-processing and translation. Prediction analysis revealed that the 67 differentially-expressed microRNAs were predicted to target 1,039 of the 1,531 differentially-expressed mRNAs, and the 1,531 differentially-expressed mRNAs were predicted to be targeted by 15 of the 67 differentially-expressed microRNAs. These 15 microRNAs showed 15-50% fold-change after alcohol treatment and were each predicted to target 60-400 mRNAs responsive to alcohol. We constructed a list of the most probable alcohol-responsive microRNA-mRNA interactions in the synapse and propose specific microRNAs which may be effective in manipulating local synaptic translation as potential treatments for alcoholism. Work supported by NIH Grants AA022557, AA13520, AA012404, RC2AA019382, AA020683

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Marchigian Sardinian alcohol-preferring rats exhibit deficient anandamide regulation of stress-induced increases in excitatory amino acid transmission in the central amygdala

[1]L.A. Natividad; [1]M.W. Buczynski; [1]M.A. Herman; [1]D. Stouffer; [2]R. Ciccocioppo; [1]M. Roberto; [1]L.H. Parsons.
[1]The Scripps Research Institute, Committee on the Neurobiology of Addictive Disorders, La Jolla, California 92037, USA; [2]Univeristy of Camerino, School of Pharmacy, Pharmacology Unit, Camerino, Italy

Marchigian Sardinian alcohol-preferring (msP) rats exhibit enhanced preference for alcohol and increased susceptibility to affective responses associated with stress and anxiety. Endogenous cannabinoid (eCB) signaling is known to play an important homeostatic role in the regulation of affective state. The current studies examined the neurochemical correlates of enhanced stress and anxiety in the central amygdala (CeA) of msP versus wildtype rats. Briefly, msP and wildtype Wistar rats (n=5-7 per group) were examined for anxiety-like behavior on the elevated plus maze following a 30-min restraint procedure. To characterize amygdalar neurochemistry, we implanted a separate cohort of animals (n=8 per group) with cannulas into the CeA region. Rats were then prepared with microdialysis probes (1 mm active membrane), and dialysate levels were retrieved in 15-min collection fractions before, during and after 30-min restraint. Similar procedures were used in a separate cohort of rats (n=8-10 per group) to examine eCB overflow. The results revealed that msP rats exhibited enhanced anxiety-like behavior than wildtypes regardless of restraint procedures. msPs also exhibited enhanced basal and stress-induced changes in the excitatory amino acid transmitters glutamate and aspartate in the CeA. In contrast, we observed that basal and stress-induced changes in anandamide (AEA) were lower in msP than wildtypes. We suggest that the enhanced stress and anxiety phenotype in