International Behavioural & Neural Genetics Society

Virtual Trainee Symposium

Hosted by: Camron Bryant, Karla Kaun, Kristin Scaplen, Antonia Savarese, Danila Cuomo, and Kristyn Borrelli

Symposium details
Date: September 23, 2020
Time: 12:00-3:00 pm EDT
Registration: IBANGS (Membership required)
Zoom info:
Society Business Meeting: 3:10-4:10 pm EDT

FEATURING:

David G. Ashbrook, PhD, Department of Genetics, Genomics and Informatics, University of Tennessee Health Science Center, Memphis, TN 38163, USA

Kristyn N. Borrelli, PhD Candidate, Graduate Program for Neuroscience, Laboratory of Addiction Genetics, Department of Pharmacology and Experimental Therapeutics and Psychiatry, Boston University School of Medicine, Boston, MA USA

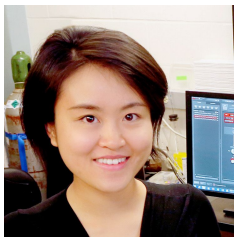
Christiann Gaines, PhD Candidate, Department of Genetics, Neuroscience Curriculum, School of Medicine, Division of Pharmacotherapy and Experimental Therapeutics, Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC USA

Alexandra Goetjen, MD/PhD Candidate, Biomedical Science PhD Program, Department of Psychiatry University of Connecticut Health Center, 263 Farmington Avenue, Farmington, CT USA

Kana Hamada, PhD Candidate, Graduate Program in Neuroscience, Center for Alcohol Research in Epigenetics, Department of Psychiatry, 4 Research Informatics Core, University of Illinois at Chicago, Chicago, IL USA

John S. Hernandez, PhD, Department of Neuroscience, Brown University, RI USA

Sam-Moon Kim, PhD, Translational Neuroscience Program, Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA. Center for Systems Neurogenetics of Addiction, The Jackson Laboratory, Bar Harbor, ME, USA.



Wanhe Li, PhD , Laboratory of Genetics, The Rockefeller University, New York, USA

Hayley Thorpe, PhD Candidate, Department of Biomedical Sciences, University of Guelph, Guelph, Ontario, Canada

Hailou Zhang, **MA**, Interdisciplinary Institute for Personalized Medicine in Brain Disorders & School of Chinese Medicine, Jinan University, Guangzhou, 510632, China

SYMPOSIUM SCHEDULE

I. GENETIC DISCOVERY AND GENOMICS (Chairs: Danila Cuomo and Kristyn Borrelli)

12:10-12:25pm:
"The interaction effects of genetic variants, diet, and mitochondrial copy number on aging and longevity in the BXD family"
David G. Ashbrook, Department of Genetics, Genomics and Informatics, University of Tennessee Health Science Center, Memphis, TN 38163, USA

12:25-12:40pm:
"Assessing the impact of compositionally distinct gut microbiotas on differences in initial cocaine sensitivity in closely related inbred mouse substrains"
Christiann Gaines, Department of Genetics, Neuroscience Curriculum, School of Medicine, Division of Pharmacotherapy and Experimental Therapeutics, Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC USA

12:40-12:55pm:
"High-Throughput Phenotyping Reveals Possible Relationships Between Circadian Rhythms and Cocaine Addiction in Genetically Diverse Mouse Populations"
Sam-Moon Kim, Translational Neuroscience Program, Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA. Center for Systems Neurogenetics of Addiction, The Jackson Laboratory, Bar Harbor, ME, USA.

12:55-1:10pm:
"Neonatal morphine (P1-14) in CFW mice induces behavioral signs of withdrawal, sex-dependent transcriptomic profiles in brainstem (P15), and altered affective and psychostimulant-induced locomotor phenotypes in adolescence"
Kristyn N. Borrelli, Laboratory of Addiction Genetics, Department of Pharmacology and Experimental Therapeutics and Psychiatry, Boston University School of Medicine, Boston, MA USA

1:10-1:25pm

II. CANDIDATE GENES, VARIANTS, AND MECHANISMS (Chair: Antonia Savarese)

1:25-1:40pm:
"Mechanisms Underlying Chronic Social Isolation Induced Sleep Loss in Drosophila"
Wanhe Li, Laboratory of Genetics, The Rockefeller University, New York, USA

1:40-1:55pm
"On baking and getting baked: Cadm2 regulates preference and consumption of THC- and cannabis oil-infused cookie dough in mice"
Hayley Thorpe, Department of Biomedical Sciences, University of Guelph, Guelph, Ontario, Canada

1:55-:2:10pm
"GABRA2 genetic variants and chromatin accessibility in induced pluripotent stem cell-derived neural cells and postmortem brain samples in the context of alcohol use disorder"
Alexandra Goetjen, Biomedical Science PhD Program, Department of Psychiatry, University of Connecticut Health Center, 263 Farmington Avenue, Farmington, CT USA

2:10-2:25pm
"Activation of ALK and STAT3 signaling in mouse prefrontal cortex and hippocampus after binge drinking"
Kana Hamada, Graduate Program in Neuroscience, Center for Alcohol Research in Epigenetics, Department of Psychiatry, 4Research Informatics Core, University of Illinois at Chicago, Chicago, IL USA

III: ADVANCES IN BEHAVIORAL MODELS AND EXPERIMENTAL TREATMENTS (Chair: Kristin Scaplen)

2:25-2:40pm
"Open bar assay: A new operant paradigm for examining motivated response and substance abuse in Drosophila Melanogaster"
John S. Hernandez, Department of Neuroscience, Brown University, RI USA

2:40-2:55pm
"The immediate and persistent antidepressant-like activity of Yueju pill in Balb/c, but not in C57BL/6J strain mice: an electrophysiological and CREB signaling study"
Hailou Zhang, Interdisciplinary Institute for Personalized Medicine in Brain Disorders & School of Chinese Medicine, Jinan University, Guangzhou, 510632, China

2:55-3:10pm
General discussion and concluding remarks

3:10-4:10pm
Society Business Meeting

Abstracts (alphabetical order of presenters)

The interaction effects of genetic variants, diet, and mitochondrial copy number on aging and longevity in the BXD family
Ingels, J.F., Roy, S., Williams, R.W., **Ashbrook, D.G.**

As the average age of the world's population increases, understanding the biology of longevity, and how healthy aging can be achieved, is of increasing importance. Basic cellular processes, such as mitochondrial function, are well conserved. The importance of mitochondrial activity in pathogenic aging has been established in studies across species. However, the interaction between genetic variants, diet, mitochondrial DNA copy number (mtDNAcn), and longevity have not been established.
We take advantage of a large cohort of females from 87 BXD strains and their C57BL/6J and DBA/2J parental strains generated at UTHSC. We followed 2157 females on a standard low-fat diet (CD, 18% calories from fat) or a widely used high-fat diet (HFD, 60% calories from fat) across their natural life span, allowing us to measure longevity. Approximately 662 females on either HFD or CD were culled at ~6, 12, 18, or 24 months of age, and a broad range of tissues extracted and stored.
Preliminary data from 384 liver samples shows significant strain and strain-by-age effects on mtDNAcn. Further, there is a significant correlation between strain mean mtDNAcn at 18 months of age and strain mean longevity, indicating a genetic linkage between these two traits. Increased mtDNAcn has been linked to healthy aging, including physical activity and cognitive function. The BXD phenome contains many measures of activity, cognition, learning, and memory. Increasing sample numbers will allow us to identify QTL, correlations between mtDNAcn measures in different tissues, and links to behavioral phenotypes of aging already measured in the BXD phenome.
Department of Genetics, Genomics and Informatics, University of Tennessee Health Science Center, Memphis, TN 38163, USA

Neonatal morphine (P1-14) in CFW mice induces behavioral signs of withdrawal, sex-dependent transcriptomic profiles in brainstem (P15), and altered affective and psychostimulant-induced locomotor phenotypes in adolescence
Kristyn N. Borrelli 1, Emily J. Yao 1, William W. Yen 2, Qiu T. Ruan 1, Julia C. Kelliher 1, Melanie M. Chen 1, Richard K. Babbs 1, Jacob A. Beierle 1, Elisha M. Wachman 3,4, Alberto Cruz-Martin 2, Camron D. Bryant 1

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The Opioid Use Disorder epidemic has led to higher incidence of Neonatal Opioid Withdrawal Syndrome (NOWS). NOWS-affected infants born to opioid-dependent mothers display body weight deficits, inconsolability, insomnia, and increased pain sensitivity. The neurobiological basis of NOWS is largely unknown, but mouse models will help facilitate mechanistic discovery. We aimed to induce repeated cycles of spontaneous opioid withdrawal during a sensitive period of neurodevelopment to understand both short- and long-term behavioral and neurodevelopmental implications of perinatal opioid exposure. We treated neonatal outbred Cartworth Farms White (CFW) mice (Swiss Webster) with morphine sulfate (MOR; 15.0 mg/kg, s.c.) once or twice daily from postnatal day 1 (P1) to P14, the approximate third trimester-equivalent of human gestation. Behavioral phenotypes were measured on P7 and P14 at 16 h post-MOR. Brainstem (containing pons and medulla) was collected on P14 and processed for transcriptome analysis via mRNA sequencing (RNA-seq). In a separate cohort, adolescent testing was performed from ~P25-36, including light/dark (~P25), elevated plus maze (~P26), Barnes Maze (~P27-31), and assessment of methamphetamine (2.0 mg/kg; intraperitoneal)-induced locomotor activity (~P32-36). MOR-induced weight deficits were observed from P2 to P14 and sustained at P21 and P50. MOR also induced a delayed self-righting latency at P4 and a female-specific delay at P7. MOR-treated females emitted more ultrasonic vocalizations (USVs) on P7, and both morphine-treated sexes showed increases in USVs on P14. Furthermore, thermal nociception via hot plate and tail withdrawal assays indicated thermal hyperalgesia in morphine mice on P7 and P14, with females showing greater hyperalgesia (tail withdrawal) on P7. MOR-treated mice also exhibited anxiety-like behavior at P21 (open field). Brainstem transcriptome pathway analysis indicated disruptions within gene networks relevant to developmental processes, food consumption, and muscle contraction in both sexes. Interestingly, there were opposing effects on ribosomal and mitochondrial gene expression by sex, as there was downregulation of genes within these networks in males and upregulation in females, potentially indicating sex-dependent modulation of metabolic function in response to perinatal MOR. During adolescence, MOR treatment was linked to decreased spatial memory performance, reduced anxiety-like behaviors, and increased locomotor activity following treatment with 2.0 mg/kg methamphetamine. Additional reward-related behavior (intracranial self-stimulation) will be assayed during adulthood (>P50) to assess long-term implications for substance abuse susceptibility.

Assessing the impact of compositionally distinct gut microbiotas on differences in initial cocaine sensitivity in closely related inbred mouse substrains

CH Gaines1,2, SA Schoenrock1, IM Carroll3, FPM de Villena1, MT Ferris1, LM Tarantino1,4

Substance use disorders are highly prevalent and impose a significant burden on affected individuals and society as a whole. Despite the prevalence of SUDs, there exist very few effective treatments. The dearth of treatments is due, in part, to gaps in our understanding of the etiology of these devastating disorders. Risk for developing an SUD is influenced by many factors including genetics, environmental influences and interactions between the two. Identifying specific genes or gene networks and understanding how the environment acts on different genetic backgrounds to increase risk would represent a significant advance to the field. Mouse models have been used extensively to perform studies aimed at identifying genetic loci implicated in addiction-like behaviors. However, identification of causal genes or SNPs has been hampered by the genetic heterogeneity present among commonly used inbred mouse strains that results in the identification of loci that span tens of megabases and contain hundreds of genes and thousands of potentially causal SNPs. To overcome this, we implemented the use of reduced complexity crosses (RCC) between closely related inbred mouse substrains. The reduced genetic complexity between substrains provides a more simplified system with which to identify and validate functional variants and their impact on complex traits.
I identified a significant difference in cocaine-induced locomotor activation between two C3H substrains, C3H/HeJ and C3H/HeNTac. A RCC of these two substrains identified only suggestive loci indicating that the striking behavioral differences observed between these substrains may be determined by non-genetic factors. I identified prominent differences in the composition of the gut microbiota between these substrains that may play a role in their divergent locomotor sensitivity to cocaine.
1Department of Genetics, 2Neuroscience Curriculum, School of Medicine, 3Department of Nutrition, Gillings School of Public Health and 4Division of Pharmacotherapy and Experimental Therapeutics, Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC
Funding support: P50 DA039841 (Center for Systems Neurogenetics of Addiction, Elissa Chesler, PI) and a Boost Grant from the UNC School of Medicine

GABRA2 genetic variants and chromatin accessibility in induced pluripotent stem cell-derived neural cells and postmortem brain samples in the context of alcohol use disorder **AM Goetjen**1, 2, M Watson2, 3, R Lieberman2, 3, K Clinton2, & J Covault1, 2, 3

Approximately 8.5% of adults in the United States are afflicted by moderate or severe alcohol use disorder (AUD). Twin studies indicate a significant genetic contribution to the risk for developing AUD. Although several candidate loci have been identified, with the exception of coding variants in the ADH1B and ALDH2 genes, little is known about the molecular effects of loci associated with AUD. We have observed a correlation between genotype of AUD-associated synonymous SNP rs279858 located in GABRA2 and transcription of GABRA2 and GABRB1 on chromosome 4p12. Publicly-available virtual circular chromatin conformation capture (4C) data on dorsolateral prefrontal cortex samples supports a hypothesis that chr4p12 GABAA gene expression is regulated in cis by a shared regulatory element. Allele-specific differences in chromatin accessibility and transcription factor binding may predispose individuals

to complex polygenic disease. The assay for transposase-accessible chromatin followed by high-throughput sequencing (ATAC-seq) allows for identification of sites of allele-specific open chromatin. Initial sequencing of one rs279858 C/C neural culture and one rs279858 T/T neural culture was supplemented with analysis of publicly-available analysis on five post-mortem subjects through the Brain Open Chromatin Atlas (BOCA). There is a neural-specific peak of open chromatin that overlaps rs1442059, a SNP in strong linkage disequilibrium with rs279858. The Genome Editing Core at UConn Health has generated homozygote iPSCs of the opposite genotype at rs1442059, and we are currently waiting on the differentiated neural samples to be sequenced so as to analyze whether altering the genotype at this locus alters transcription of GABRA2 and GABRB1.

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2Department of Psychiatry, UConn School of Medicine, 263 Farmington Avenue, Farmington, CT 06030 3Neuroscience Area of Concentration, Biomedical Science PhD Program, University of Connecticut Health Center, 263 Farmington Avenue, Farmington, CT 06030
This work was supported by NIAAA grant P60 AA03510 to the UConn Health Alcohol Research Center, the Connecticut Department of Health Regenerative Medicine Fund grant 15-RMB-UCHC-04 to JC, and NIAAA grant F30 AA027153 to AMG.

Activation of ALK and STAT3 signaling in mouse prefrontal cortex and hippocampus after binge drinking

Hamada, K.1,2, Ferguson, L.3, Mayfield, R. D.3, Krishnan, H. R.,2 Maienschein-Cline, M.4, and Lasek, A. W.2

Alcohol use disorder (AUD) is a difficult disorder to treat. Identifying relevant signaling pathways in the brain may be useful for finding new pharmacological targets to treat AUD. The receptor tyrosine kinase ALK activates the transcription factor STAT3 in response to ethanol exposure in vitro. Here, we demonstrate ALK activation and upregulation of known STAT3 target genes (Socs3, Gfap, and Tnfrsf1a) in the prefrontal cortex (PFC) and ventral hippocampus (vHPC) of mice after 4 days of binge-like ethanol drinking. To investigate the behavioral relevance of activated STAT3, we treated mice with a STAT3 inhibitor, stattic, and observed that they drank less ethanol compared with vehicle-treated mice. Finally, to identify novel ethanol-induced target genes downstream of ALK-STAT3, we analyzed the NIH LINCS L1000 database for gene signature overlap between ALK inhibitor (alectinib and NVP-TAE684) and STAT3 inhibitor (niclosamide) treatments on cell lines. This signature was then compared to genes that were differentially expressed in the PFC of mice after binge-like drinking. We found 95 unique gene candidates and examined them for STAT3 binding motifs in their promoters. Fifty-seven of the 95 genes had STAT3 motifs. We validated by qPCR that expression of putative STAT3 target genes Nr1h2, Smarcc1, Smarca4, and Gpnmb were increased in the PFC or vHPC after binge-like drinking. Together these results demonstrate activation of the ALK-STAT3 signaling pathway in the brain after binge-like ethanol consumption, identify putative novel

ethanol-responsive STAT3 target genes, and suggest that STAT3 inhibition may be a potential method to reduce binge drinking in humans.
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Funding Support: NIAAA: U01 AA020912 (AWL), P50 AA022538 (AWL), T32AA026577 (KH), and U01 AA020926 (RDM)

Open bar assay: A new operant paradigm for examining motivated response and substance abuse in Drosophila Melanogaster
Hernandez, J.S. 1 , Glenn, E. 1 , Catalano, J. 1,2, and Kaun, K.R.1 1 Department of

Neuroscience, Brown University, RI. 2 Molecular Pharmacology and Physiology Graduate Program, Brown University, RI Escalation of alcohol self-administration facilitates the transition from alcohol use to compulsive drinking, a worldwide biomedical concern. Investigating the circuits and neural dynamics underlying escalation of alcohol consumption is critical for developing more effective treatments for alcohol use and abuse disorders. We developed a 3-day operant paradigm to evaluate selfadministration patterns of a pharmacologically-relevant dose of volatilized ethanol (50% EtOH) and compared those behaviors to self-administration patterns for appetitive food odors (e.g., apple cider vinegar; ACV). We then evaluated subtle behavioral changes in escalating selfadministration using a combined computer vision and machine learning approaches. Our preliminary data suggests that, similar to mammals, individual variation in selfadministration behavior occurs with consecutive exposure sessions. Approximately 30% of flies escalate 50% EtOH self-administration. This contrasts significantly with self-administration seen with appetitive odors such as ACV (15% of flies escalate) and 3% EtOH (0.08% escalate), and aversive odor benzaldehyde (.08% escalate). This data lays a behavioral groundwork to subsequently investigate variability in identified circuits contributing to alcohol and substance use disorders. Comparing the behavioral self-administration patterns for natural appetitive and aversive stimuli to intoxicating doses of ethanol uniquely primes us to examine how natural and drug reward preference manifests in the nervous system.

High-Throughput Phenotyping Reveals Possible Relationships Between Circadian Rhythms and Cocaine Addiction in Genetically Diverse Mouse Populations.
Sam-Moon Kim1,2, Chelsea A Vadnie[1], Vivek M. Philip[2], Leona H. Gagnon[2], Kodavali V. Chowdari[1], Sarah A Schoenrock[2,3], Lisa M Tarantino[2,3], Price E Dickson[2], Troy D Wilcox[2], Michael R Leonardo[2], Elissa J. Chesler[2], Colleen A. McClung[1,2,*] and Ryan W. Logan[1,2,*].

Circadian rhythms and reward-related pathways mutually interact and their variability is driven by genetics. Diverse Outbred (DO) and Collaborative Cross (CC) mice are powerful tools for examining the genetics of complex traits because their higher genetic and phenotypic diversity than conventional mouse strains. In order to understand the genetic link between circadian rhythms and cocaine addiction, we established a high-throughput system to measure cellular

rhythms using primary fibroblasts in DO/CC mice and their founders composed of five common-inbred and three wild-derived strains. Among the founders, we observed significant strain and sex differences in rhythm period, phase, amplitude and robustness with strong heritability. Extreme phenotypic differences were observed between A/J and CAST/EiJ in fibroblast and behavioral rhythms, where A/J had the longest period and CAST/EiJ had the shortest. Our preliminary correlation analysis suggested that the mouse strains with longer periods and with reduced amplitude displayed more relapse-like and drug-seeking behaviors in cocaine self-administration (IVSA) respectively. In CC strains, CC004/TauUnc displayed significantly higher addiction-related behaviors in cocaine-sensitization and IVSA relative to CC041/TauUnc, along with the observation of longer circadian period and lower amplitude in CC041/TauUnc than CC004/TauUnc. Furthermore, we measured fibroblast rhythms in 329 DO mice, which displayed greater circadian phenotypic diversity than the founders-80% of founders compared to only 25% DO mice displayed periods of ~24hours. Collectively, our study demonstrates that genetic diversity contributes to phenotypic variability in circadian rhythms and our high-throughput data in those mice is powerful for elucidating the genetic mechanisms underlying circadian rhythms and addiction-related phenotypes.
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Funding support: P50 DA039841 (Colleen McClung)

Mechanisms Underlying Chronic Social Isolation Induced Sleep Loss in Drosophila
W Li1, Z Wang1, S Syed2, S Lincoln1, J O'Neil1, MW Young1

Social isolation and loneliness have potent effects on public health. The recent outbreak of COVID-19 is posing a tremendous mental health threat to our society as social distancing, social isolation and quarantines are the musts to control the pandemic. Research in social psychology suggests that compromised sleep quality is a key factor linking persistent loneliness to adverse health conditions. Though experimental manipulations have been widely applied to studying sleep/wakefulness control in animal models, how normal sleep is perturbed by social isolation is unknown. Here we report that chronic, but not acute social isolation reduces sleep in Drosophila. We use quantitative behavioral analysis and transcriptome profiling to differentiate acute vs. chronic social isolation brain states. Despite the animal's uninterrupted access to food, chronic social isolation alters metabolic gene expression and induces a brain state that signals starvation. Chronically isolated animals exhibit sleep-loss accompanied by overconsumption of food, which resonates with anecdotal findings of loneliness-associated hyperphagia in humans. Chronic social isolation reduces sleep and promotes feeding through neural activities in the peptidergic fan-shaped body neurons of the fly. Artificial activation of these neurons causes misperception of acute social isolation as chronic social isolation and thus results in sleep loss.

These results together present a mechanistic link between chronic social isolation, metabolism and sleep, addressing a long-standing call for efficient animal models focused on loneliness.
1Laboratory of Genetics, The Rockefeller University, New York, United States, 2Department Physics, University of Miami, Coral Gables, United States
Funding Support: NIH grants NS053087 and GM054339. Fellowships to Wanhe Li from the Leon Levy Foundation, the Jane Coffin Childs Memorial Fund and the Grass Foundation.

On baking and getting baked: Cadm2 regulates preference and consumption of THC- and cannabis oil-infused cookie dough in mice
HHA Thorpe1, AM Talhat1, JY Khokhar1

It is estimated that 3.9% of the global population uses cannabis annually. Polymorphisms in Cell Adhesion Molecule 2 (CADM2), a gene associated with impulsivity, information processing, and substance use, were recently implicated in cannabis use initiation, though the causal relationship between variation in this gene and cannabis use vulnerability has yet to be elucidated. In the present study, we used a Cadm2-/- mouse to investigate the role of CADM2 in Δ9-tetrahydrocannabinol (THC) and cannabis oil preference. Adult Cadm2-/- and wildtype mice were presented with two cookie dough balls containing escalating doses THC or vehicle for 30 minutes daily. In a separate pilot study, Cadm2-/-, Cadm2+/-, and wildtype mice were delivered cannabis oil in place of THC. Compared to wildtype controls, Cadm2-/- mice displayed lower preference for THC- and cannabis-infused dough and consumed more dough overall. Associative learning, evaluated through cued and contextual fear conditioning, was also suggested to be impaired in Cadm2-/- mice. The novel edible cannabis preference test utilized by this study can be used to assess genotype-dependent motivation for THC and cannabis oil edibles in mice. Lower cannabis dough preference in Cadm2-/- mice suggests that Cadm2 is important in the motivation to consume THC and cannabis edibles, and that knockout of Cadm2 may reduce engagement in risky behaviours and produce learning impairments. These findings support evidence that CADM2 polymorphisms may underly cannabis use initiation risk, possibly through trait impulsivity.
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Funding Support: Discovery Grant from the Natural Sciences and Engineering Research Council award (RGPIN-2019-05121) to JYK

The immediate and persistent antidepressant-like activity of Yueju pill in Balb/c, but not in C57BL/6J strain mice: an electrophysiological and CREB signaling study
Hailou Zhang1, Tong Zhou2, Yan Sun1, Wenda Xue2, Gang Chen1

Depression and its pharmacological treatment are significantly influenced by genetics. We previously revealed that between two outbred strain mice, there was a similar immediate antidepressant activity of a single dose of Yueju or ketamine, but the persistent activity was different between strains. Here, we assessed the difference in antidepressant effect of Yueju in two common inbred strain and investigated the underlying PKA-CREB signaling and related electrophysiological basis. We found a single dose of Yueju produced immediate and persistent

antidepressant-like effect only in Balb/c strain mice, but not in C57BL/6J mice. Moreover, brain derived neurotrophic factor (BDNF) protein expression rapidly increased in hippocampus of Balb/c mice at 30 min or 24 hr after Yueju, without alteration in C57BL/6J mice. The PKA-CREB signaling that regulates BDNF and synaptic protein PSD95 displayed the similar strain-dependent expression pattern. We measured the long-term potentiation (LTP) in the hippocampus after Yueju in both strains. LTP was enhanced only in Balb/c or not in C57BL/6J mice. Finally, mice were treated with H-89 (PKA inhibitor) before or after Yueju, and the effect of H-89 was also tested on ketamine. The immediate and persistent antidepressant- effect of Yueju were blunted regardless of the time of H-89 treatment. In contrast, pre-treatment of H-89 only blunted the persistent, but not immediate. antidepressant effect of ketamine. The present study suggests that the strain-dependent immediate and persistent antidepressant-like effect of Yueju involved in activating PKA-CREB signaling and subsequent LTP. Initial activation of PKA-CREB signaling regulates maintenance of ketamine's antidepressant activity.
Keywords: depression, Yueju pill, PKA, CREB, LTP.
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