



Cover legend: This image shows parvalbumin (yellow), β -catenin (red), and DAPI (blue) in an APC cKO mouse. In their article, Ryner et al. show that the maturation and survival of parvalbumin interneurons are disrupted in a model of early life epilepsy, known as infantile spasms. Inhibitory circuits are prominently shaped by development, so early life seizures may disrupt parvalbumin interneuron maturation. Conversely, inhibitory circuit dysfunction may contribute to seizure initiation, creating a potentially vicious cycle. By combining genetic models of infantile spasms, with anatomical and electrophysiological approaches, the authors shed new light on potential mechanisms of pathogenesis in a model of devastating early life epilepsy. For more information, see the article by Ryner et al. (pages 1422–1440). Cover image: Rachael Ryner and Mary Sommer.

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Articles

CELLULAR/MOLECULAR

Spontaneous Activity of the Local GABAergic Synaptic Network Causes Irregular Neuronal Firing in the External Globus Pallidus

James A. Jones,¹ Matthew H. Higgs,² Erick Olivares,¹ Jacob Peña,¹ and Charles J. Wilson¹

¹Department of Neuroscience, Developmental and Regenerative Biology, University of Texas at San Antonio, San Antonio, Texas 78249 ²Aging & Metabolism Research Program, Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma 73104

Autonomously firing GABAergic neurons in the external globus pallidus (GPe) form a local synaptic network. In slices, most GPe neurons receive a continuous inhibitory synaptic barrage from 1 or 2 presynaptic GPe neurons. We measured the barrage's effect on the firing rate and regularity of GPe neurons in male and female mice using perforated patch recordings. Silencing the firing of parvalbumin-positive (PV⁺) GPe neurons by activating genetically expressed Archaelhodopsin current increased the firing rate and regularity of PV⁺ neurons. In contrast, silencing Npas1⁺ GPe neurons with Archaelhodopsin had insignificant effects on Npas1⁺ neuron firing. Blocking spontaneous GABAergic synaptic input with gabazine reproduced the effects of silencing PV⁺ neuron firing on the firing rate and regularity of Npas1⁺ neurons and had similar effects on PV⁺ neuron firing. To simulate the barrage, we constructed conductance waveforms for dynamic clamp based on experimentally measured inhibitory postsynaptic conductance trains from 1 or 2 unitary local connections. The resulting inhibition replicated the effect on firing seen in the intact active network in the slice. We then increased the number of unitary inputs to match estimates of local network connectivity *in vivo*. As few as 5 unitary inputs produced large increases in firing irregularity. The firing rate was also reduced initially, but PV⁺ neurons exhibited a slow spike-frequency adaptation that partially restored the rate despite sustained inhibition. We conclude that the irregular firing pattern of GPe neurons *in vivo* is largely due to the ongoing local inhibitory synaptic barrage produced by the spontaneous firing of other GPe neurons.

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Mechanisms That Underlie Expression of Estradiol-Induced Excitatory Synaptic Potentiation in the Hippocampus Differ between Males and Females

Anant Jain and Catherine S. Woolley

Department of Neurobiology, Northwestern University, Evanston, Illinois 60208

17 β -estradiol (E2) is synthesized in the hippocampus of both sexes and acutely potentiates excitatory synapses in each sex. Previously, we found that the mechanisms for initiation of E2-induced synaptic potentiation differ between males and females, including in the molecular signaling involved. Here, we used electrical stimulation and two-photon glutamate uncaging in hippocampal slices from adult male and female rats to investigate whether the downstream consequences of distinct molecular signaling remain different between the sexes or converge to the same mechanism(s) of expression of potentiation. This showed that synaptic activity is necessary for expression of E2-induced potentiation in females but not males, which paralleled a sex-specific requirement in females for calcium-permeable AMPARs (cpAMPARs) to stabilize potentiation. Nonstationary fluctuation analysis of two-photon evoked unitary synaptic currents showed that the postsynaptic component of E2-induced potentiation occurs either through an increase in AMPAR conductance or in nonconductive properties of AMPARs (number of channels $\times$ open probability) and never both at the same synapse. In females, most synapses (76%) were potentiated via increased AMPAR conductance, whereas in males, more synapses (60%) were potentiated via an increase in nonconductive AMPAR properties. Inhibition of cpAMPARs eliminated E2-induced synaptic potentiation in females, whereas some synapses in males were unaffected by cpAMPAR inhibition; these synapses in males potentiated exclusively via increased AMPAR nonconductive properties. This sex bias in expression mechanisms of E2-induced synaptic potentiation underscores the concept of latent sex differences in mechanisms of synaptic plasticity in which the same outcome in each sex is achieved through distinct underlying mechanisms.

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DEVELOPMENT/PLASTICITY/REPAIR

Postsynaptic NMDA Receptor Expression Is Required for Visual Corticocollicular Projection Refinement in the Mouse Superior Colliculus

Kristy O. Johnson,^{1,2} Leeor Harel,¹ and Jason W. Triplett^{1,2,3,4}

¹Center for Neuroscience Research, Children's National Research Institute, Washington, DC 20010 ²Institute for Biomedical Sciences, George Washington University School of Medicine, Washington, DC 20037 ³Department of Pediatrics, George Washington University School of Medicine, Washington, DC 20037 ⁴Department of Pharmacology and Physiology, George Washington University School of Medicine, Washington, DC 20037

Efficient sensory processing of spatial information is facilitated through the organization of neuronal connections into topographic maps of space. In integrative sensory centers, converging topographic maps must be aligned to merge spatially congruent information. The superior colliculus (SC) receives

topographically ordered visual inputs from retinal ganglion cells (RGCs) in the eye and layer 5 neurons in the primary visual cortex (L5-V1). Previous studies suggest that RGCs instruct the alignment of later-arriving L5-V1 inputs in an activity-dependent manner. However, the molecular mechanisms underlying this remain unclear. Here, we explored the role of NMDA receptors in visual map alignment in the SC using a conditional genetic knockout approach. We leveraged a novel knock-in mouse line that expresses tamoxifen-inducible Cre recombinase under the control of the *Tal1* gene (*Tal1^{CreERT2}*), which we show allows for specific recombination in the superficial layers of the SC. We used *Tal1^{CreERT2}* mice of either sex to conditionally delete the obligate GluN1 subunit of the NMDA receptor (SC-cKO) during the period of visual map alignment. We observed a significant disruption of L5-V1 axon terminal organization in the SC of SC-cKO mice. Importantly, retinocollicular topography was unaffected in this context, suggesting that alignment is also disrupted. Time-course experiments suggest that NMDA receptors may play a critical role in the refinement of L5-V1 inputs in the SC. Together, these data implicate NMDA receptors as critical mediators of activity-dependent visual map alignment in the SC.

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SYSTEMS/CIRCUITS

A Cross-Species Neuroimaging Study of Sex Chromosome Dosage Effects on Human and Mouse Brain Anatomy

Elisa Guma,¹ Antoine Beauchamp,^{2,3,4} Siyuan Liu,¹ Elizabeth Levitis,¹ Liv S. Clasen,¹ Erin Torres,¹ Jonathan Blumenthal,¹ Francois Lalonde,¹ Lily R. Qiu,^{2,3} Haley Hrcncir,⁶ Allan MacKenzie-Graham,⁵ Xia Yang,⁶ Arthur P. Arnold,⁶ Jason P. Lerch,^{2,3,4,7} and Armin Raznahan¹

¹Section on Developmental Neurogenetics, Human Genetics Branch, National Institute of Mental Health, Bethesda, 20892, Maryland ²Mouse Imaging Centre, Toronto, Ontario M5T 3H7, Canada ³The Hospital for Sick Children, Toronto, Ontario M5G 1X8, Canada ⁴Department of Medical Biophysics, University of Toronto, Toronto, Ontario M5G 1L7, Canada ⁵Department of Neurology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California 90095 ⁶Department of Integrative Biology and Physiology, University of California, Los Angeles, Los Angeles, California 90095 ⁷Wellcome Centre for Integrative Neuroimaging, University of Oxford, Oxford, OX3 9DU, United Kingdom

All eutherian mammals show chromosomal sex determination with contrasting sex chromosome dosages (SCDs) between males (XY) and females (XX). Studies in transgenic mice and humans with sex chromosome trisomy (SCT) have revealed direct SCD effects on regional mammalian brain anatomy, but we lack a formal test for cross-species conservation of these effects. Here, we develop a harmonized framework for comparative structural neuroimaging and apply this to systematically profile SCD effects on regional brain anatomy in both humans and mice by contrasting groups with SCT (XXY and XYY) versus XY controls. Total brain size was substantially altered by SCT in humans (significantly decreased by XXY and increased by XYY), but not in mice. Robust and spatially convergent effects of XXY and XYY on regional brain volume were observed in humans, but not mice, when controlling for global volume differences. However, mice do show subtle effects of XXY and XYY on regional volume, although there is not a general spatial convergence in these effects within mice or between species. Notwithstanding this general lack of conservation in SCT effects, we detect several brain regions that show overlapping effects of XXY and XYY both within and between species (cerebellar, parietal, and orbitofrontal cortex), thereby nominating high priority targets for future translational dissection of SCD effects on the mammalian brain. Our study introduces a generalizable framework for comparative neuroimaging in humans and mice and applies this to achieve a cross-species comparison of SCD effects on the mammalian brain through the lens of SCT.

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Excitatory Projections from the Prefrontal Cortex to Nucleus Accumbens Core D1-MSNs and κ Opioid Receptor Modulate Itch-Related Scratching Behaviors

Xiao-Bo Wu, Qian Zhu, Ming-Hui Gao, Sheng-Xiang Yan, Pan-Yang Gu, Peng-Fei Zhang, Meng-Lin Xu, and Yong-Jing Gao

Institute of Pain Medicine and Special Environmental Medicine, Co-innovation Center of Neuroregeneration, Nantong University, Jiangsu 226019, China

Itch is an uncomfortable and complex sensation that elicits the desire to scratch. The nucleus accumbens (NAc) activity is important in driving sensation, motivation, and emotion. Excitatory afferents from the medial prefrontal cortex (mPFC), amygdala, and hippocampus are crucial in tuning the activity of dopamine receptor D1-expressing and D2-expressing medium spiny neurons (Drd1-MSN and Drd2-MSN) in the NAc. However, a cell-type and neural circuitry-based mechanism of the NAc underlying acute itch remains unclear. We found that acute itch induced by compound 48/80 (C48/80) decreased the intrinsic membrane excitability in Drd1-MSNs, but not in Drd2-MSNs, in the NAc core of male mice. Chemogenetic activation of Drd1-MSNs alleviated C48/80-induced scratching behaviors but not itch-related anxiety-like behaviors. In addition, C48/80 enhanced the frequency of spontaneous EPSCs (sEPSCs) and reduced the paired-pulse ratio (PPR) of electrical stimulation-evoked EPSCs in Drd1-MSNs. Furthermore, C48/80 increased excitatory synaptic afferents to Drd1-MSNs from the mPFC, not from the basolateral amygdala (BLA) or ventral hippocampus (vHipp). Consistently, the intrinsic excitability of mPFC-NAc projecting pyramidal neurons was increased after C48/80 treatment. Chemogenetic inhibition of mPFC-NAc excitatory synaptic afferents relieved the scratching behaviors. Moreover, pharmacological activation of κ opioid receptor (KOR) in the NAc core suppressed C48/80-induced scratching behaviors, and the modulation of KOR activity in the NAc resulted in the changes of presynaptic excitatory inputs to Drd1-MSNs in C48/80-treated mice. Together, these results reveal the neural plasticity in synapses of NAc Drd1-MSNs from the mPFC underlying acute itch and indicate the modulatory role of the KOR in itch-related scratching behaviors.

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Infralimbic Projections to the Nucleus Accumbens Shell and Amygdala Regulate the Encoding of Cocaine Extinction Learning

Kelle E. Nett,¹ Alexa R. Zimbelman,² Matthew S. McGregor,¹ Vanessa Alizo Vera,² Molly R. Harris,² and Ryan T. LaLumiere^{1,2,3}

¹Interdisciplinary Neuroscience Program, University of Iowa, Iowa City, Iowa 52242 ²Department of Psychological and Brain Sciences, University of Iowa, Iowa City, Iowa 52242 ³Iowa Neuroscience Institute, University of Iowa, Iowa City, Iowa 52242

Prior evidence indicates that the infralimbic cortex (IL) mediates the ongoing inhibition of cocaine seeking following self-administration and extinction training in rats, specifically through projections to the nucleus accumbens shell (NAshell). Our own data indicate that IL activity immediately following an unreinforced lever press is critical for encoding the extinction contingencies in such procedures. Whether extinction encoding requires activity in the IL exclusively or also activity in its outputs, such as those to the NAshell and amygdala, is unknown. To address this issue, we used a closed-loop optogenetic approach in female and male Sprague Dawley rats to silence IL–NAshell or IL–amygdala activity following an unreinforced lever press during extinction training. Optical illumination (20 s) was given either immediately after a lever press or following a 20 s delay. IL–NAshell inhibition immediately following an unreinforced lever press increased lever pressing during extinction training and impaired retention of extinction learning, as assessed during subsequent extinction sessions without optical inhibition. Likewise, IL–amygdala inhibition given in the same manner impaired extinction retention during sessions without inhibition. Control experiments indicate that critical encoding of extinction learning does not require activity in these pathways beyond the initial 20 s post-lever press period, as delayed IL–NAshell and IL–amygdala inhibition had no effect on extinction learning. These results suggest that a larger network extending from the IL to the NAshell and amygdala is involved in encoding extinction contingencies following cocaine self-administration.

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Chemical Flavorants in Vaping Products Alter Neurobiology in a Sex-Dependent Manner to Promote Vaping-Related Behaviors

Skylar Y. Cooper, Clay V. Willis, Montana R. Richardson, Sean P. Hill, Sheavonnie K. Wright, Morgan B. Elmore, Zach B. Mitchell, Astrid K. González Castro, and Brandon J. Henderson

Department of Biomedical Sciences, Joan C. Edwards School of Medicine, Marshall University, Huntington, West Virginia 25701

Electronic nicotine delivery systems (ENDS) are distinctly different from combustible cigarettes because of the availability of flavor options. Subjective measures have been used to demonstrate that adults and adolescents prefer flavors for various reasons; (1) they are pleasing and (2) they mask the harshness of nicotine. Despite this, there have been few investigations into the molecular interactions that connect chemical flavorants to smoking or vaping-related behaviors. Here, we investigated the effects of three chemical flavorants (hexyl acetate, ethyl acetate, and methylbutyl acetate) that are found in green apple (GA) ENDS e-liquids but are also found in other flavor categories. We used a translationally relevant vapor self-administration mouse model and observed that adult male and female mice self-administered GA flavorants in the absence of nicotine. Using $\alpha 4$ -mCherry $\alpha 6$ -GFP nicotinic acetylcholine receptor (nAChR) mice, we observed that mice exposed to GA flavorants exhibited a sex-specific increase (upregulation) of nAChRs that was also brain-region specific. Electrophysiology revealed that mice exposed to GA flavorants exhibited enhanced firing of ventral tegmental area dopamine neurons. Fast-scan cyclic voltammetry revealed that electrically stimulated dopamine release in the nucleus accumbens core is increased in mice that are exposed to GA flavorants. These effects were similarly observed in the medial habenula. Overall, these findings demonstrate that ENDS flavors alone change neurobiology and may promote vaping-dependent behaviors in the absence of nicotine. Furthermore, the flavorant-induced changes in neurobiology parallel those caused by nicotine, which highlights the fact that nonmenthol flavorants may contribute to or enhance nicotine reward and reinforcement.

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Learning-Induced Odor Modulation of Neuronal Activity in Auditory Cortex

Omri David Gilday¹ and Adi Mizrahi^{1,2}

¹The Edmond and Lily Safra Center for Brain Sciences, The Hebrew University of Jerusalem, Jerusalem 91904, Israel, ²Department of Neurobiology, The Hebrew University of Jerusalem, Jerusalem, 91904, Israel

Sensory cortices, even of primary regions, are not purely unisensory. Rather, cortical neurons in sensory cortex show various forms of multisensory interactions. While some multisensory interactions naturally co-occur, the combination of others will co-occur through experience. In real life, learning and experience will result in conjunction with seemingly disparate sensory information that ultimately becomes behaviorally relevant, impacting perception, cognition, and action. Here we describe a novel auditory discrimination task in mice, designed to manipulate the expectation of upcoming trials using olfactory cues. We show that, after learning, female mice display a transient period of several days during which they exploit odor-mediated expectations for making correct decisions. Using two-photon calcium imaging of single neurons in auditory cortex (ACx) during behavior, we found that the behavioral effects of odor-mediated expectations are accompanied by an odor-induced modulation of neuronal activity. Further, we find that these effects are manifested differentially, based on the response preference of individual cells. A significant portion of effects, but not all, are consistent with a predictive coding framework. Our data show that learning novel odor–sound associations evoke changes in ACx. We suggest that behaviorally relevant multisensory environments mediate contextual effects as early as ACx.

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Mechanisms Underlying the Recruitment of Inhibitory Interneurons in Fictive Swimming in Developing *Xenopus laevis* Tadpoles

Andrea Ferrario,^{1,3} Valentina Saccomanno,² Hong-Yan Zhang,² Roman Borisyuk,¹ and Wen-Chang Li²

¹Department of Mathematics and Statistics, University of Exeter, Exeter EX4 4QF, United Kingdom ²School of Psychology & Neuroscience, University of St Andrews, St Andrews KY16 9JP, United Kingdom ³Biorobotics Laboratory, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland

Developing spinal circuits generate patterned motor outputs while many neurons with high membrane resistances are still maturing. In the spinal cord of hatching frog tadpoles of unknown sex, we found that the firing reliability in swimming of inhibitory interneurons with commissural and ipsilateral ascending axons was negatively correlated with their cellular membrane resistance. Further analyses showed that neurons with higher resistances had outward rectifying properties, low firing thresholds, and little delay in firing evoked by current injections. Input synaptic currents these neurons received during swimming, either compound, unitary current amplitudes, or unitary synaptic current numbers, were scaled with their membrane resistances, but their own synaptic outputs were correlated with membrane resistances of their postsynaptic partners. Analyses of neuronal dendritic and axonal lengths and their activities in swimming and cellular input resistances did not reveal a clear correlation pattern. Incorporating these electrical and synaptic properties into a computer swimming model produced robust swimming rhythms, whereas randomizing input synaptic strengths led to the breakdown of swimming rhythms, coupled with less synchronized spiking in the inhibitory interneurons. We conclude that the recruitment of these developing interneurons in swimming can be predicted by cellular input resistances, but the order is opposite to the motor-strength-based recruitment scheme depicted by Henneman's size principle. This form of recruitment/integration order in development before the emergence of refined motor control is progressive potentially with neuronal acquisition of mature electrical and synaptic properties, among which the scaling of input synaptic strengths with cellular input resistance plays a critical role.

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BEHAVIORAL/COGNITIVE

Rapid Processing of Invisible Fearful Faces in the Human Amygdala

Yingying Wang,¹ Lu Luo,² Guanpeng Chen,^{3,4,5} Guoming Luan,^{6,7,8} Xiongfei Wang,⁶ Qian Wang,^{3,4,5} and Fang Fang^{3,4,5}

¹Department of Psychology and Behavioral Sciences, Zhejiang University, Hangzhou 310028, Zhejiang, China ²School of Psychology, Beijing Sport University, Beijing 100084, China ³School of Psychological and Cognitive Sciences and Beijing Key Laboratory of Behavior and Mental Health, Peking University, Beijing 100871, China ⁴International Development Group (IDG)/McGovern Institute for Brain Research, Peking University, Beijing 100871, China ⁵Peking-Tsinghua Center for Life Sciences, Peking University, Beijing 100871, China ⁶Department of Functional Neurosurgery, Sanbo Brain Hospital, Capital Medical University, Beijing 1000932, China ⁷Beijing Key Laboratory of Epilepsy, Epilepsy Center, Sanbo Brain Hospital, Capital Medical University, Beijing 100093, China ⁸Beijing Institute for Brain Disorders, Beijing 100069, China ⁹Department of Clinical Neuropsychology, Sanbo Brain Hospital, Capital Medical University, Beijing 100093 China

Rapid detection of a threat or its symbol (e.g., fearful face), whether visible or invisible, is critical for human survival. This function is suggested to be enabled by a subcortical pathway to the amygdala independent of the cortex. However, conclusive electrophysiological evidence in humans is scarce. Here, we explored whether the amygdala can rapidly encode invisible fearful faces. We recorded intracranial electroencephalogram (iEEG) responses in the human (both sexes) amygdala to faces with fearful, happy, and neutral emotions rendered invisible by backward masking. We found that a short-latency intracranial event-related potential (iERP) in the amygdala, beginning 88 ms poststimulus onset, was preferentially evoked by invisible fearful faces relative to invisible happy or neutral faces. The rapid iERP exhibited selectivity to the low spatial frequency (LSF) component of the fearful faces. Time-frequency iEEG analyses further identified a rapid amygdala response preferentially for LSF fearful faces at the low gamma frequency band, beginning 45 ms poststimulus onset. In contrast, these rapid responses to invisible fearful faces were absent in cortical regions, including early visual areas, the fusiform gyrus, and the parahippocampal gyrus. These findings provide direct evidence for the existence of a subcortical pathway specific for rapid fear detection in the amygdala and demonstrate that the subcortical pathway can function without conscious awareness and under minimal influence from cortical areas.

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Linking Impulsivity to Activity Levels in Pre-Supplementary Motor Area during Sequential Gambling

Allan Lohse,^{1,2} Annemette Løkkegaard,² Hartwig R. Siebner,^{1,2,3} and David Meder¹

¹Danish Research Centre for Magnetic Resonance, Centre for Functional and Diagnostic Imaging and Research, Copenhagen University Hospital—Amager and Hvidovre, 2650 Hvidovre, Denmark ²Department of Neurology, Copenhagen University Hospital Bispebjerg, 2400 Copenhagen, Denmark

³Institute for Clinical Medicine, Faculty of Medical and Health Sciences, University of Copenhagen, DK-2200 Copenhagen, Denmark

Impulsivity refers to the tendency to act prematurely or without forethought, and excessive impulsivity is a key problem in many neuropsychiatric disorders. Since the pre-supplementary motor area (pre-SMA) has been implicated in inhibitory control, this region may also contribute to impulsivity. Here, we examined whether functional recruitment of pre-SMA may contribute to risky choice behavior (state impulsivity) during sequential gambling and its relation to self-reported trait impulsivity. To this end, we performed task-based functional MRI (fMRI) after low-frequency (1 Hz) repetitive transcranial magnetic

stimulation (rTMS) of the pre-SMA. We expected low-frequency rTMS to modulate task-related engagement of the pre-SMA and, hereby, tune the tendency to make risky choices. Twenty-four healthy volunteers (12 females; age range, 19–52 years) received real or sham-rTMS on separate days in counterbalanced order. Thereafter, participants performed a sequential gambling task with concurrently increasing stakes and risk during whole-brain fMRI. In the sham-rTMS session, self-reported trait impulsivity scaled positively with state impulsivity (riskier choice behavior) during gambling. The higher the trait impulsivity, the lower was the task-related increase in pre-SMA activity with increasingly risky choices. Following real-rTMS, low-impulsivity participants increased their preference for risky choices, while the opposite was true for high-impulsivity participants, resulting in an overall decoupling of trait impulsivity and state impulsivity during gambling. This rTMS-induced behavioral shift was mirrored in the rTMS-induced change in pre-SMA activation. These results provide converging evidence for a causal link between the level of task-related pre-SMA activity and the propensity for impulsive risk-taking behavior in the context of sequential gambling.

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NEUROBIOLOGY OF DISEASE

Cortical Parvalbumin-Positive Interneuron Development and Function Are Altered in the APC Conditional Knockout Mouse Model of Infantile and Epileptic Spasms Syndrome

Rachael F. Ryner,^{1,2} Isabel D. Derera,¹ Moritz Armbruster,¹ Anar Kansara,¹ Mary E. Sommer,¹ Antonella Pirone,¹ Farzad Noubary,³ Michele Jacob,¹ and Chris G. Dulla¹

¹Department of Neuroscience, Tufts University School of Medicine, Boston, Massachusetts 02111 ²Cell, Molecular, and Developmental Biology Graduate Program, Tufts Graduate School of Biomedical Sciences, Boston, Massachusetts 02111 ³Department of Health Sciences, Bouvé College of Health Sciences, Northeastern University, Boston, Massachusetts 02115

Infantile and epileptic spasms syndrome (IESS) is a childhood epilepsy syndrome characterized by infantile or late-onset spasms, abnormal neonatal EEG, and epilepsy. Few treatments exist for IESS, clinical outcomes are poor, and the molecular and circuit-level etiologies of IESS are not well understood. Multiple human IESS risk genes are linked to Wnt/ β -catenin signaling, a pathway that controls developmental transcriptional programs and promotes glutamatergic excitation via β -catenin's role as a synaptic scaffold. We previously showed that deleting adenomatous polyposis coli (APC), a component of the β -catenin destruction complex, in excitatory neurons (APC cKO mice, APC^{fl/fl} x CaMKII α^{Cre}) increased β -catenin levels in developing glutamatergic neurons and led to infantile behavioral spasms, abnormal neonatal EEG, and adult epilepsy. Here, we tested the hypothesis that the development of GABAergic interneurons (INs) is disrupted in APC cKO male and female mice. IN dysfunction is implicated in human IESS, is a feature of other rodent models of IESS, and may contribute to the manifestation of spasms and seizures. We found that parvalbumin-positive INs (PV⁺ INs), an important source of cortical inhibition, were decreased in number, underwent disproportionate developmental apoptosis, and had altered dendrite morphology at P9, the peak of behavioral spasms. PV⁺ INs received excessive excitatory input, and their intrinsic ability to fire action potentials was reduced at all time points examined (P9, P14, P60). Subsequently, GABAergic transmission onto pyramidal neurons was uniquely altered in the somatosensory cortex of APC cKO mice at all ages, with both decreased IPSC input at P14 and enhanced IPSC input at P9 and P60. These results indicate that inhibitory circuit dysfunction occurs in APC cKOs and, along with known changes in excitation, may contribute to IESS-related phenotypes.

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A Gating Mutation in Ryanodine Receptor Type 2 Rescues Phenotypes of Alzheimer's Disease Mouse Models by Upregulating Neuronal Autophagy

Hua Zhang,¹ Caitlynn Knight,¹ S.R. Wayne Chen,² and Ilya Bezprozvanny^{1,3}

¹Department of Physiology, UT Southwestern Medical Center, Dallas, Texas 75390 ²Department of Physiology and Pharmacology, University of Calgary, Calgary, Alberta T2N 1N4, Canada ³Laboratory of Molecular Neurodegeneration, St. Petersburg State Polytechnical University, St. Petersburg 195251, Russian Federation

It is well established that ryanodine receptors (RyanRs) are overactive in Alzheimer's disease (AD), and it has been suggested that inhibition of RyanR is potentially beneficial for AD treatment. In the present study, we explored a potential connection between basal RyanR activity and autophagy in neurons. Autophagy plays an important role in clearing damaged organelles and long-lived protein aggregates, and autophagy dysregulation occurs in both AD patients and AD animal models. Autophagy is known to be regulated by intracellular calcium (Ca²⁺) signals, and our results indicated that basal RyanR2 activity in hippocampal neurons inhibited autophagy through activation of calcineurin and the resulting inhibition of the AMPK (AMP-activated protein kinase)–ULK1 (unc-51-like autophagy-activating kinase 1) pathway. Thus, we hypothesized that increased basal RyanR2 activity in AD may lead to the inhibition of neuronal autophagy and accumulation of β -amyloid. To test this hypothesis, we took advantage of the RyanR2-E4872Q knock-in mouse model (EQ) in which basal RyanR2 activity is reduced because of shortened channel open time. We discovered that crossing EQ mice with the APPKI and APPPS1 mouse models of AD (both males and females) rescued amyloid accumulation and LTP impairment in these mice. Our results revealed that reduced basal activity of RyanR2-EQ channels disinhibited the autophagic pathway and led to increased amyloid clearance in these models. These data indicated a potential pathogenic outcome of RyanR2 overactivation in AD and also provided additional targets for therapeutic intervention in AD. Basal activity of ryanodine receptors controls neuronal autophagy and contributes to development of the AD phenotype.

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