Astrocytes Speed Action Potential Propagation

Courtney Sobieski, Xiaoping Jiang, Devon C. Crawford, and Steven Mennerick

Glia affect neural circuits in numerous ways. Microglia strip synapses and clear debris after injury; oligodendrocytes form myelin, which regulates axon conduction velocity and limits sprouting; and astrocytes direct blood flow to active circuits, provide nutrients and growth factors, regulate extracellular ion concentrations, guide neurite growth, promote synaptogenesis, stabilize dendritic spines, and encapsulate synapses to limit the spread of neurotransmitters. Accumulating evidence suggests that astrocytes also influence axonal conduction, for example, by releasing glutamate and ATP along the axon and by regulating extracellular potassium levels at nodes of Ranvier (reviewed in Fields et al. 2015 Neuron 86: 374). Sobieski et al. add to this evidence by showing that action potential shape and propagation speed differ in isolated hippocampal neurons grown in contact with (+) or without (no-) astrocytes.

The first clue that astrocytes affected axonal propagation was the unusual shape of autaptic EPSCs evoked by current injection into no-astrocyte neurons. Not only were the time to peak greater and the peak amplitude lower in no-astrocyte neurons than in + astrocyte neurons, but a large-scale asynchrony involving multiple peaks was apparent in EPSCs of no-astrocyte neurons. Importantly, the timing of local peaks within EPSCs was largely invariant across trials, their amplitudes were much larger than quantal amplitudes, and they were insensitive to calcium chelators, suggesting they did not result from delayed release of single vesicles triggered by persistent calcium elevation in axonal terminals. Instead, the multiple peaks seemed to result from asynchronous arrival of action potentials at different terminals. Indeed, action potential propagation speed was significantly reduced in no-astrocyte neurons, which would likely cause release at distal terminals to be delayed relative to release more proximal to the soma. In addition, the spike width was greater in distal axons of no-astrocyte neurons than in + astrocyte neurons.

These data suggest that astrocytes regulate the rate of action potential propagation and thus the synchrony of release across synaptic terminals. Thus, astrocytes may have a profound impact on neuronal processes that rely on precise spike timing, such as dendritic integration and coincidence detection, spike-timing-dependent synaptic plasticity, and the binding of features represented in different brain regions through synchronous activity.

GABAergic neurons (red) generated in the MGE (bottom right) migrate tangentially to populate the developing cerebral cortex. See Skorput et al. for details.

Gestational Ethanol Exposure Increases Inhibition in mPFC

Alexander G. J. Skorput, Vivek P. Gupta, Pamela W. L. Yeh, and Hermes H. Yeh

Prenatal alcohol exposure alters brain development, leading to long-lasting physical, behavioral, and/or cognitive effects. The type and severity of these effects depends on the timing, duration, and magnitude of exposure, but impaired executive functions, including deficits in working memory, response inhibition, and cognitive flexibility (the ability to shift problem-solving strategies), are common even in people with the mildest forms of fetal alcohol spectrum disorder.

The medial prefrontal cortex (mPFC) is a key mediator of executive control, and behavioral flexibility requires intact functioning of GABAergic neurons in this brain area. Previous work (Cuzon et al. 2008 J Neurosci 28:1854) revealed that when pregnant mice consumed moderate levels of ethanol during the first two weeks of pregnancy, GABAergic neurons in embryos migrated more quickly from their site of origin in the medial ganglionic eminence (MGE) to the cortex, increasing the density of GABAergic neurons in cortex at embryonic day 14.5 (E14.5).

To further investigate the effects of prenatal ethanol exposure on the development of inhibitory circuitry, Skorput et al. used a binge-like ethanol exposure regimen restricted to the period of peak interneuron migration (E13.5–16.5). This treatment increased by ~35% the density of MGE-derived neurons in the mPFC, and the increase persisted into young adulthood. Inhibitory input to mPFC layer V pyramidal cells was also greater in mice exposed to ethanol in utero, and the ratio of inhibitory and excitatory inputs (I/E) was 3-fold greater in ethanol-exposed mice than in controls.

Mice exposed to ethanol in utero also showed impaired behavioral flexibility: Although they were as proficient as controls in learning the location of an escape hole in a circular maze (a hippocampus-dependent task), they were slower to find the hole when it was moved, largely because they continued to search in the original location. The extent to which this deficit resulted from the shift in I/E balance remains to be demonstrated, however.

The period of ethanol exposure used in this study is gestationally equivalent to the middle of the first trimester in humans. At this time, women may be unaware that they are pregnant. Therefore, the results reported here underscore the admonition that women who might be pregnant should limit alcohol consumption.
Inhibition of Group I Metabotropic Glutamate Receptors Reverses Autistic-Like Phenotypes Caused by Deficiency of the Translation Repressor eIF4E Binding Protein 2
Argel Aguilar-Valles, Edna Matta-Camacho, Arkady Khoutorsky, Christos Gkogkas, Karim Nader, Jean-Claude Lacaille, and Nahum Sonenberg

HuR Mediates Changes in the Stability of AChR β-Subunit mRNAs after Skeletal Muscle Denervation
Olivier R. Joassard, Guy Bélanger, Jennifer Karmouch, John A. Lunde, Anu H. Shukla, Angèle Chopard, Claire Legay, and Bernard J. Jasmin

Synaptotagmin-7 Is Essential for Ca²⁺-Triggered Delayed Asynchronous Release But Not for Ca²⁺-Dependent Vesicle Priming in Retinal Ribbon Synapses
Fujun Luo, Taulant Bacaj, and Thomas C. Südhof

Oligophrenin-1 Connects Exocytotic Fusion to Compensatory Endocytosis in Neuroendocrine Cells
Sébastien Houy, Catherine Estay-Ahumada, Pauline Croisé, Valérie Calco, Anne-Marie Haeberlé, Yannick Bailly, Pierre Billuart, Nicolas Vitale, Marie-France Bader, Stéphane Ory, and Stéphane Gasman

Inositol Hexakisphosphate Kinase-3 Regulates the Morphology and Synapse Formation of Cerebellar Purkinje Cells via Spectrin/Adducin
Chenglai Fu, Jing Xu, Ruo-Jing Li, Joshua A. Crawford, A. Basit Khan, Ting Martin Ma, Jiyoung Y. Cha, Adele M. Snowman, Mikhail V. Pletnikov, and Solomon H. Snyder

Loss of Local Astrocyte Support Disrupts Action Potential Propagation and Glutamate Release Synchrony from Unmyelinated Hippocampal Axon Terminals In Vitro
Courtney Sobieski, Xiaoping Jiang, Devon C. Crawford, and Steven Mennerick

Neurotensin Induces Presynaptic Depression of D₂ Dopamine Autoreceptor-Mediated Neurotransmission in Midbrain Dopaminergic Neurons
Elisabeth Piccart, Nicholas A. Courtney, Sarah Y. Branch, Christopher P. Ford, and Michael J. Beckstead
Thalamic WNT3 Secretion Spatiotemporally Regulates the Neocortical Ribosome Signature and mRNA Translation to Specify Neocortical Cell Subtypes
Matthew L. Kraushar, Barbara Viljetic, H. R. Sagara Wijeratne, Kevin Thompson, Xinfu Jiao, Jack W. Pike, Vera Medvedeva, Matthias Groszer, Megeerditch Kiledjian, Ronald P. Hart, and Mladen-Roko Rasin

Expressing Constitutively Active Rheb in Adult Neurons after a Complete Spinal Cord Injury Enhances Axonal Regeneration beyond a Chondroitinase-Treated Glial Scar
Di Wu, Michelle C. Klaw, Theresa Connors, Nikolai Kholodilov, Robert E. Burke, and Veronica J. Tom

Mechanosensory Genes Pkd1 and Pkd2 Contribute to the Planar Polarization of Brain Ventricular Epithelium
Shinya Ohata (大畑慎也), Vicente Herranz-Pérez, Jin Nakatani (中谷 仁), Alessandra Boletta, José Manuel García-Verdugo, and Arturo Álvarez-Buylla

Posterior Parietal Cortex Encoding of Dynamic Hand Force Underlying Hand–Object Interaction
Simone Ferrari-Toniolo, Federica Visco-Comandini, Odysseas Papazachariadis, Roberto Caminiti, and Alexandra Battaglia-Mayer

Functional Microarchitecture of the Mouse Dorsal Inferior Colliculus Revealed through In Vivo Two-Photon Calcium Imaging
Oliver Barnstedt, Peter Keating, Yves Weissenberger, Andrew J. King, and Johannes C. Dahmen

Interspike Intervals Reveal Functionally Distinct Cell Populations in the Medial Entorhinal Cortex
Patrick Latuske, Oana Toader, and Kevin Allen

Functional Connectivity of Insula, Basal Ganglia, and Prefrontal Executive Control Networks during Hypoglycemia in Type 1 Diabetes
Nicolas R. Bolo, Gail Musen, Donald C. Simonson, Lisa D. Nickerson, Veronica L. Flores, Tamar Siracusa, Brandon Hager, In Kyoon Lyoo, Perry F. Renshaw, and Alan M. Jacobson

Synaptic Basis for Differential Orientation Selectivity between Complex and Simple Cells in Mouse Visual Cortex
Ya-tang Li, Bao-hua Liu, Xiao-lin Chou, Li I. Zhang, and Huizhong W. Tao

Glutamate Receptors in the Central Nucleus of the Amygdala Mediate Cisplatin-Induced Malaise and Energy Balance Dysregulation through Direct Hindbrain Projections
Amber L. Alhadeff, Ruby A. Holland, Alexandra Nelson, Harvey J. Grill, and Bart C. De Jonghe

Neural Signatures of Conscious Face Perception in an Inattentional Blindness Paradigm
Juliet P. Shafto and Michael A. Pitts

Payoff Information Biases a Fast Guess Process in Perceptual Decision Making under Deadline Pressure: Evidence from Behavior, Evoked Potentials, and Quantitative Model Comparison
Sharareh Noorbaloocchi, Dahlia Sharon, and James L. McClelland

Intrahippocampal Anisomycin Impairs Spatial Performance on the Morris Water Maze
Jonathan D. Dubue, Ty L. McKinney, Dallas Treit, and Clayton T. Dickson
Opponent Identity Influences Value Learning in Simple Games
Timothy J. Vickery, Matthew R. Kleinman, Marvin M. Chun, and Daeyeol Lee

Persistent Interneuronopathy in the Prefrontal Cortex of Young Adult Offspring Exposed to Ethanol In Utero
Alexander G. J. Skorput, Vivek P. Gupta, Pamela W. L. Yeh, and Hermes H. Yeh

The Effect of Body Posture on Brain Glymphatic Transport
Hedok Lee, Lulu Xie, Mei Yu, Hongyi Kang, Tian Feng, Rashid Deane, Jean Logan, Maiken Nedergaard, and Helene Benveniste

Correction: The article ”Chronic Nicotine Activates Stress/Reward-Related Brain Regions and Facilitates the Transition to Compulsive Alcohol Drinking” by Rodrigo M. Leão, Fábio C. Cruz, Leandro F. Vendruscolo, Giordano de Guglielmo, Marian L. Logrip, Cleopatra S. Planeta, Bruce T. Hope, George F. Koob, and Olivier George appeared on pages 6241–6253 of the April 15, 2015 issue. A correction for this article appears on page 11169.
Inhibition of Group I Metabotropic Glutamate Receptors Reverses Autistic-Like Phenotypes Caused by Deficiency of the Translation Repressor eIF4E Binding Protein 2

Argel Aguilar-Valles,1,2 Edna Matta-Camacho,2 Arkady Khoutorsky,2 Christos Gkogkas,2,4 Karim Nader,3 Jean-Claude Lacaille,1,* and Nahum Sonenberg2,*

1Department of Neurosciences and Groupe de Recherche sur le Système Nerveux Central, Université de Montréal, Montréal, Québec H3C 3J7, Canada, 2Department of Biochemistry and Goodman Cancer Centre, McGill University, Montréal, Québec H3A 1A2, Canada, 3Department of Psychology, McGill University, Montréal, Québec H3A 1B1, Canada, and 4Patrick Wild Centre and Centre for Integrative Physiology, University of Edinburgh, Edinburgh EH8 9XD, United Kingdom

Exacerbated mRNA translation during brain development has been linked to autism spectrum disorders (ASDs). Deletion of the eukaryotic initiation factor 4E (eIF4E)-binding protein 2 gene (Eif4ebp2), encoding the suppressor of mRNA translation initiation 4E-BP2, leads to an imbalance in excitatory-to-inhibitory neurotransmission and ASD-like behaviors. Inhibition of group I metabotropic glutamate receptors (mGluRs) mGluR1 and mGluR5 reverses the autistic phenotypes in several ASD mouse models. Importantly, these receptors control synaptic physiology via activation of mRNA translation. We investigated the potential reversal of autistic-like phenotypes in Eif4ebp2−/− mice by using antagonists of mGluR1 (JNJ16259685) or mGluR5 (fenobam). Augmented hippocampal mGluR-induced long-term depression (LTD; or chemically induced mGluR-LTD) in Eif4ebp2−/− mice was rescued by mGluR1 or mGluR5 antagonists. While rescue by mGluR5 inhibition occurs through the blockade of a protein synthesis-dependent component of LTD, normalization by mGluR1 antagonists requires the activation of protein synthesis. Synaptically induced LTD was deficient in Eif4ebp2−/− mice, and this deficit was not rescued by group I mGluR antagonists. Furthermore, a single dose of mGluR1 (0.3 mg/kg) or mGluR5 (3 mg/kg) antagonists in vivo reversed the deficits in social interaction and repetitive behaviors (marble burying) in Eif4ebp2−/− mice. Our results demonstrate that Eif4ebp2−/− mice serve as a relevant model to test potential therapies for ASD symptoms. In addition, we provide substantive evidence that the inhibition of mGluR1/mGluR5 is an effective treatment for physiological and behavioral alterations caused by exacerbated mRNA translation initiation.

The Journal of Neuroscience, August 5, 2015 • 35(31):10949–10962

Articles

CELLULAR/MOLECULAR

HuR Mediates Changes in the Stability of AChR β-Subunit mRNAs after Skeletal Muscle Denervation

Olivier R. Joassard,1 Guy Bélanger,1 Jennifer Karmouch,2 John A. Lunde,1 Anu H. Shukla,1 Angèle Chopard,1 Claire Legay,1 and Bernard J. Jasmin1

1Department of Cellular and Molecular Medicine and Centre for Neuromuscular Disease, Faculty of Medicine, University of Ottawa, Ottawa, Ontario K1H 8M5, Canada, and 2CESEM, CNRS UMR 8194, University of Paris Descartes, F75270 Paris Cédex, France

Acetylcholine receptors (AChRs) are heteromeric membrane proteins essential for neurotransmission at the neuromuscular junction. Previous work showed that muscle denervation increases expression of AChR mRNAs due to transcriptional activation of AChR subunit genes. However, it remains possible that post-transcriptional mechanisms are also involved in controlling the levels of AChR mRNAs following denervation. We examined whether post-transcriptional events indeed regulate AChR β-subunit mRNAs in response to denervation. First, in vitro stability assays revealed that the half-life of AChR β-subunit mRNAs was increased in the presence of denervated muscle protein extracts. A bioinformatics analysis revealed the existence of a conserved AU-rich element (ARE) in the 3′-untranslated region (UTR) of AChR β-subunit mRNA. Furthermore, denervation of mouse muscle injected with a luciferase reporter construct containing the AChR β-subunit 3′UTR, caused an increase in luciferase activity. By contrast, mutation of this ARE prevented this increase. We also observed that denervation increased expression of the RNA-binding protein human antigen R (HuR) and induced its translocation to the cytoplasm. Importantly, HuR binds to endogenous AChR β-subunit transcripts in cultured myotubes and in vivo, and this binding is increased in denervated versus innervated muscles. Finally, p38 MAPK, a pathway known to activate HuR, was induced following denervation as a result of MKK3/6 activation and a decrease in MKP-1 expression, thereby leading to an increase in the stability of AChR β-subunit transcripts. Together, these results demonstrate the important contribution of post-transcriptional events in regulating AChR β-subunit mRNAs and point toward a central role for HuR in mediating synaptic gene expression.

The Journal of Neuroscience, August 5, 2015 • 35(31):10949–10962
Synaptotagmin-7 Is Essential for Ca\textsuperscript{2+} -Triggered Delayed Asynchronous Release But Not for Ca\textsuperscript{2+} -Dependent Vesicle Priming in Retinal Ribbon Synapses

Fujun Luo, Taulant Bacaj, and Thomas C. Südhof
Department of Molecular and Cellular Physiology and Howard Hughes Medical Institute, Stanford University, Stanford, California 94304-5453

Most synapses release neurotransmitters in two phases: (1) a fast synchronous phase lasting a few milliseconds; and (2) a delayed “asynchronous” phase lasting hundreds of milliseconds. Ca\textsuperscript{2+} triggers fast synchronous neurotransmitter release by binding to synaptotagmin-1, synaptotagmin-2, or synaptotagmin-9, but how Ca\textsuperscript{2+} triggers delayed asynchronous release has long remained enigmatic. Recent results suggested that consistent with the Ca\textsuperscript{2+} -sensor function of synaptotagmin-7 in neuroendocrine exocytosis, synaptotagmin-7 also functions as a Ca\textsuperscript{2+} sensor for synaptic vesicle exocytosis but operates during delayed asynchronous release. Puzzlingly, a subsequent study postulated that synaptotagmin-7 is not a Ca\textsuperscript{2+} sensor for release but mediates Ca\textsuperscript{2+} -dependent vesicle repriming after intense stimulation. To address these issues, we here analyzed synaptic transmission at rod bipolar neuron–AII amacrine cell synapses in acute mouse retina slices as a model system. Using paired recordings, we show that knock-out of synaptotagmin-7 selectively impairs delayed asynchronous release but not fast synchronous release. Delayed asynchronous release was blocked in wild-type synapses by intracellular addition of high concentrations of the slow Ca\textsuperscript{2+} -chelator EGTA, but EGTA had no effect in synaptotagmin-7 knock-out neurons because delayed asynchronous release was already impaired. Moreover, direct measurements of vesicle repriming failed to uncover an effect of the synaptotagmin-7 knock-out on vesicle repriming. Our data demonstrate that synaptotagmin-7 is selectively essential for Ca\textsuperscript{2+} -dependent delayed asynchronous release in retinal rod bipolar cell synapses, that its function can be blocked by simply introducing a slow Ca\textsuperscript{2+} buffer into the cells, and that synaptotagmin-7 is not required for normal vesicle repriming.

The Journal of Neuroscience, August 5, 2015 • 35(31):11056–11067

Oligophrenin-1 Connects Exocytic Fusion to Compensatory Endocytosis in Neuroendocrine Cells

Sébastien Houy,\textsuperscript{1,4} Catherine Estay-Ahumada,\textsuperscript{*} Pauline Croisé,\textsuperscript{1} Valérie Calco,\textsuperscript{2} Anne-Marie Haeberlé,\textsuperscript{1} Yannick Bailly,\textsuperscript{1} Pierre Billuart,\textsuperscript{1} Nicolas Vitale,\textsuperscript{1} Marie-France Bader,\textsuperscript{1} Stéphane Ory,\textsuperscript{1} and Stéphane Gasman\textsuperscript{1,†}
\textsuperscript{1}Institut des Neurosciences Cellulaires et Intégratives, Centre National de la Recherche Scientifique, UPR 3212, and Université de Strasbourg, 67084 Strasbourg, France, and \textsuperscript{2}Institut Cochin, Département Génétique et Développement, INSERM U 1016, CNRS UMR 8104, Faculté de Médecine de Paris Descartes, 75014 Paris, France

Oligophrenin-1 (OPHN1) is a protein with multiple domains including a Rho family GTPase-activating (Rho-GAP) domain, and a Bin-Amphiphysin-Rvs (BAR) domain. Involved in X-linked intellectual disability, OPHN1 has been reported to control several synaptic functions, including synaptic plasticity, synaptic vesicle trafficking, and endocytosis. In neuroendocrine cells, hormones and neuropeptides stored in large dense core vesicles (secretory granules) are released through calcium-regulated exocytosis, a process that is tightly coupled to compensatory endocytosis, allowing secretory granule recycling. We show here that OPHN1 is expressed and mainly localized at the plasma membrane and in the cytosol in chromaffin cells from adrenal medulla. Using carbon fiber amperometry, we found that exocytosis is impaired at the late stage of membrane fusion in \textit{Ophn1} knock-out mice and OPHN1-silenced bovine chromaffin cells. Experiments performed with ectopically expressed OPHN1 mutants indicate that OPHN1 requires its Rho-GAP domain to control fusion pore dynamics. On the other hand, compensatory endocytosis assessed by measuring dopamine-β-hydroxylase (secretory granule membrane) internalization is severely inhibited in \textit{Ophn1} knock-out chromaffin cells. This inhibitory effect is mimicked by the expression of a truncated OPHN1 mutant lacking the BAR domain, demonstrating that the BAR domain implicates OPHN1 in granule membrane recapture after exocytosis. These findings reveal for the first time that OPHN1 is a bifunctional protein that is able, through distinct mechanisms, to regulate and most likely link exocytosis to compensatory endocytosis in chromaffin cells.

The Journal of Neuroscience, August 5, 2015 • 35(31):11024–11033

Inositol Hexakisphosphate Kinase-3 Regulates the Morphology and Synapse Formation of Cerebellar Purkinje Cells via Spectrin/Adducin

Chenglai Fu,\textsuperscript{1} Jing Xu,\textsuperscript{1} Ruo-Jing Li,\textsuperscript{2} Joshua A. Crawford,\textsuperscript{3} A. Basit Khan,\textsuperscript{1} Ting Martin Ma,\textsuperscript{1} Jiyoung Y. Cha,\textsuperscript{1} Adele M. Snowman,\textsuperscript{1} Mikhail V. Pletnikov,\textsuperscript{3} and Solomon H. Snyder\textsuperscript{1,2,3}
\textsuperscript{1}The Solomon H. Snyder Department of Neuroscience, \textsuperscript{2}Departments of Pharmacology and Molecular Sciences, and \textsuperscript{3}Departments of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

The inositol hexakisphosphate kinases (IP6Ks) are the principal enzymes that generate inositol pyrophosphates. There are three IP6Ks (IP6K1, 2, and 3). Functions of IP6K1 and IP6K2 have been substantially delineated, but little is known of IP6K3’s role in normal physiology, especially in the brain. To elucidate functions of IP6K3, we generated mice with targeted deletion of IP6K3. We demonstrate that IP6K3 is highly concentrated in the brain in cerebellar Purkinje cells. IP6K3 physiologically binds to the cytoskeletal proteins adducin and spectrin, whose mutual interactions are perturbed in IP6K3-null mutants. Consequently, IP6K3 knock-out cerebellum manifest abnormalities in Purkinje cell structure and synapse number, and the mutant mice display deficits in motor learning and coordination. Thus, IP6K3 is a major determinant of cytoskeletal disposition and function of cerebellar Purkinje cells.

The Journal of Neuroscience, August 5, 2015 • 35(31):11056–11067
Loss of Local Astrocyte Support Disrupts Action Potential Propagation and Glutamate Release Synchrony from Unmyelinated Hippocampal Axon Terminals In Vitro

Courtney Sobieski,¹,² Xiaoping Jiang,¹ Devon C. Crawford,¹,² and Steven Mennerick¹,³,⁴
¹Department of Psychiatry, ²Graduate Program in Neurosciences, ³Department of Anatomy and Neurobiology, and ⁴Taylor Family Institute for Innovative Psychiatric Research, Washington University School of Medicine, St. Louis, Missouri 63110

Neuron–astrocyte interactions are critical for proper CNS development and function. Astrocytes secrete factors that are pivotal for synaptic development and function, neuronal metabolism, and neuronal survival. Our understanding of this relationship, however, remains incomplete due to technical hurdles that have prevented the removal of astrocytes from neuronal circuits without changing other important conditions. Here we overcame this obstacle by growing solitary rat hippocampal neurons on microcultures that were comprised of either an astrocyte bed (+ astrocyte) or a collagen bed (− astrocyte) within the same culture dish. — Astrocyte autaptic evoked EPSCs, but not IPSCs, displayed an altered temporal profile, which included increased synaptic delay, increased time to peak, and severe glutamate release asynchrony, distinct from previously described quantal asynchrony. Although we observed minimal alteration of the somatically recorded action potential waveform, action potential propagation was altered. We observed a longer latency between somatic initiation and arrival at distal locations, which likely explains asynchronous EPSC peaks, and we observed broadening of the axonal spike, which likely underlies changes to evoked EPSC onset. No apparent changes in axon structure were observed, suggesting altered axonal excitability. In conclusion, we propose that local astrocyte support has an unappreciated role in maintaining glutamate release synchrony by disturbing axonal signal propagation.


Neurotensin Induces Presynaptic Depression of D2 Dopamine Autoreceptor-Mediated Neurotransmission in Midbrain Dopaminergic Neurons

Elisabeth Piccart,¹ Nicholas A. Courtney,² Sarah Y. Branch,¹ Christopher P. Ford,³ and Michael J. Beckstead¹,²
¹Department of Physiology and ²Center for Biomedical Neuroscience, University of Texas Health Science Center at San Antonio, San Antonio, Texas 78229-3904, and ³Department of Physiology and Biophysics, Case Western Reserve University School of Medicine, Cleveland, Ohio 44106-4970

Increased dopaminergic signaling is a hallmark of severe mesencephalic pathologies such as schizophrenia and psychostimulant abuse. Activity of midbrain dopaminergic neurons is under strict control of inhibitory D2 autoreceptors. Application of the modulatory peptide neurotensin (NT) to midbrain dopaminergic neurons transiently increases activity by decreasing D2 dopamine autoreceptor function, yet little is known about the mechanisms that underlie long-lasting effects. Here, we performed patch-clamp electrophysiology and fast-scan cyclic voltammetry in mouse brain slices to determine the effects of NT on dopamine autoreceptor-mediated neurotransmission. Application of the active peptide fragment NT8−13 produced synaptic depression that exhibited short- and long-term components. Sustained depression of D2 neurotransmission in Midbrain Dopaminergic Neurons


DEVELOPMENT/PLASTICITY/REPAIR

Thalamic WNT3 Secretion Spatiotemporally Regulates the Neocortical Ribosome Signature and mRNA Translation to Specify Neocortical Cell Subtypes

Matthew L. Kraushar,¹ Barbara Viljetic,¹ H. R. Sagara Wijeratne,¹ Kevin Thompson,¹ Xinfu Jiao,² Jack W. Pike,¹ Vera Medvedeva,¹ Matthias Groszer,¹ Megerditch Kiledjian,² Ronald P. Hart,² and Mladen-Roko Rasin¹
¹Department of Neuroscience & Cell Biology, Robert Wood Johnson Medical School and ²Department of Cell Biology & Neuroscience, Rutgers University, Piscataway, New Jersey 08854, and ³Inserm, UMR-S839, Sorbonne Universités, Pierre et Marie Curie Université Paris 06, Institut du Fer à Moulin, Paris 75005, France

Neocortical development requires tightly controlled spatiotemporal gene expression. However, the mechanisms regulating ribosomal complexes and the timed specificity of neocortical mRNA translation are poorly understood. We show that active mRNA translation complexes (polysomes) contain ribosomal protein subsets that undergo dynamic spatiotemporal rearrangements during mouse neocortical development. Ribosomal protein specificity within polysome complexes is regulated by the arrival of in-growing thalamic axons, which secrete the morphogen Wingless-related MMTV (mouse mammary tumor virus) integration site 3 (WNT3). Thalamic WNT3 release during midneurogenesis promotes a change in the levels of Ribosomal protein L7 in polysomes, thereby regulating neocortical translation machinery specificity. Furthermore, we present an RNA sequencing dataset analyzing mRNAs that dynamically associate with polysome complexes as neocortical development progresses, and thus may be regulated spatiotemporally at the level of translation. Thalamic WNT3 regulates neocortical translation of two such mRNAs, Foxp2 and Apc, to promote FOXP2
The Journal of Neuroscience, August 5, 2015 • 35(31):11153–11168

Expression of PCP genes may enable targeted and rapid spatiotemporal control of ribosome composition and selective mRNA translation in complex developing systems like the neocortex.

**Expressing Constitutively Active Rheb in Adult Neurons after a Complete Spinal Cord Injury Enhances Axonal Regeneration beyond a Chondroitinase-Treated Glial Scar**

Di Wu, Michelle C. Klaw, Theresa Connors, Nikolai Kholidilov, Robert E. Burke, and Veronica J. Tom

1Department of Neurobiology and Anatomy, Drexel University College of Medicine, Philadelphia, Pennsylvania 19129, and Departments of 2Neurology and 3Pathology and Cell Biology, Columbia University, New York, New York 10032

A spinal cord injury (SCI), CNS axons fail to regenerate, resulting in permanent deficits. This is due to: (1) the presence of inhibitory molecules, e.g., chondroitin sulfate proteoglycans (CSPG), in the glial scar at the lesion; and (2) the diminished growth capacity of adult neurons. We sought to determine whether expressing a constitutively active form of the GTPase Rheb (caRheb) in adult neurons after a complete SCI in rats improves intrinsic growth potential to result in axon regeneration out of a growth-supportive peripheral nerve graft (PNG) into the SCI cavity. We also hypothesized that treating the glial scar with chondroitinase ABC (ChABC), which digests CSPG, would further allow caRheb-transduced neurons to extend axons across the distal graft interface. We found that targeting this pathway at a clinically relevant post-SCI time point improves both sprouting and regeneration of axons. CaRheb increased the number of axons, but not the number of neurons, that projected into the PNG, indicative of augmented sprouting. We also saw that caRheb enhanced sprouting far rostral to the injury. CaRheb not only increased growth rostral and into the graft, it also resulted in significantly more regrowth of axons across a ChABC-treated scar into caudal spinal cord. CaRheb + neurons had higher levels of growth-associated-43, suggestive of a newly identified mechanism for mTOR-mediated enhancement of regeneration. Thus, we demonstrate for the first time that simultaneously addressing intrinsic and scar-associated, extrinsic impediments to regeneration results in significant regrowth beyond an extremely challenging, complete SCI site.

The Journal of Neuroscience, August 5, 2015 • 35(31):11068 –11080

**Mechanosensory Genes Pkd1 and Pkd2 Contribute to the Planar Polarization of Brain Ventricular Epithelium**

Shinya Ohata, Vicente Herranz-Pérez, Jin Nakatani, Alessandra Boletta, José Manuel García-Verdugo, and Arturo Álvarez-Buylla

1Department of Neurological Surgery, and Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research, University of California, San Francisco (UCSF), San Francisco, California 94143, 2Laboratorio de Neurobiología Comparada, Instituto Cavanilles, Universidad de Valencia, CIBERNED, 46980 Valencia, Spain, 3Unidad Mixta de Esclerosis Múltiple y Neurorrehabilitación, IIS Hospital La Fe, 46026 Valencia, Spain, 4Biomedical MR Science Division, Shiga University of Medical Science, Ohtsu, Shiga 520-2192, Japan, and 5Division of Genetics and Cell Biology, San Raffaele Scientific Institute, 20132 Milan, Italy

Directional beating of ependymal (E) cells’ cilia in the walls of the ventricles in the brain is essential for proper CSF flow. E cells display two forms of planar cell polarity (PCP): rotational polarity of individual cilium and translational polarity (asymmetric positioning of cilia in the apical area). The orientation of individual E cells varies according to their location in the ventricular wall (location-specific PCP). It has been hypothesized that hydrodynamic forces on the apical surface of radial glia cells (RGCs), the embryonic precursors of E cells, could guide location-specific PCP in the ventricular epithelium. However, the detection mechanisms for these hydrodynamic forces have not been identified. Here, we show that the mechanosensory proteins polycystic kidney disease 1 (Pkd1) and Pkd2 are present in primary cilia of RGCs. Ablation of Pkd1 or Pkd2 in Nestin-CrePkd1flox/flox or Nestin-CrePkd2flox/flox mice, affected PCP development in RGCs and E cells. Early shear forces on the ventricular epithelium may activate Pkd1 and Pkd2 in primary cilia of RGCs to properly polarize RGCs and E cells. Consistently, Pkd1, Pkd2, or primary cilia on RGCs were required for the proper asymmetric localization of the PCP protein Vangl2 in E cells’ apical area. Analyses of single- and double-heterozygous mutants for Pkd1 and/or Vangl2 suggest that these genes function in the same pathway to establish E cells’ PCP. We conclude that Pkd1 and Pkd2 mechanosensory proteins contribute to the development of brain PCP and prevention of hydrocephalus.

The Journal of Neuroscience, August 5, 2015 • 35(31):11153–11168

**Systems/Circuits**

**Posterior Parietal Cortex Encoding of Dynamic Hand Force Underlying Hand–Object Interaction**

Simone Ferrari-Toniolo, Federica Visco-Comandini, Odysseas Papazachariadis, Roberto Caminiti, and Alexandra Battaglia-Mayer

Department of Physiology and Pharmacology, Sapienza University of Rome, 00185 Rome, Italy

Major achievements of primate evolution are skilled hand–object interaction and tool use, both in part dependent on parietal cortex expansion. We recorded spiking activity from macaque inferior parietal cortex during directional manipulation of an isometric tool, which required the application of hand forces to control a cursor’s motion on a screen. In areas PF/PFG, the activity of ~70% neurons was modulated by the hand force necessary to implement the desired target motion, reflecting an inverse
model, rather than by the intended motion of the visual cursor (forward model). The population vector matched the direction and amplitude of the instantaneous force increments over time. When exposed to a new force condition, that obliged the monkey to change the force output to successfully bring the cursor to the final target, the activity of a consistent subpopulation of neurons changed in an orderly fashion and, at the end of a “Wash-out” session, retained memory of the new learned association, at the service of predictive control of force. Our findings suggest that areas PFG/PF represent a crucial node of the distributed control of hand force, by encoding instantaneous force variations and serving as a memory reservoir of hand dynamics required for object manipulation and tool use. This is coherent with previous studies in humans showing the following: (1) impaired adaptation to a new force field under TMS parietal perturbation; (2) defective control of direction of hand force after parietal lesion; and (3) fMRI activation of parietal cortex during object manipulation requiring control of fine hand forces.

The Journal of Neuroscience, August 5, 2015 • 35(31):10899 – 10910

Functional Microarchitecture of the Mouse Dorsal Inferior Colliculus Revealed through In Vivo Two-Photon Calcium Imaging

Oliver Barnstedt,1,2 Peter Keating,1 Yves Weissenberger,1 Andrew J. King,1 and Johannes C. Dahmen1

1Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford OX1 3PT, United Kingdom, and 2Centre for Neural Circuits and Behaviour, University of Oxford, Oxford OX1 3SR, United Kingdom

The inferior colliculus (IC) is an obligatory relay for ascending auditory inputs from the brainstem and receives descending input from the auditory cortex. The IC comprises a central nucleus (CNIC), surrounded by several shell regions, but the internal organization of this midbrain nucleus remains incompletely understood. We used two-photon calcium imaging to study the functional microarchitecture of both neurons in the mouse dorsal IC and corticocollicular axons that terminate there. In contrast to previous electrophysiological studies, our approach revealed a clear functional distinction between the CNIC and the dorsal cortex of the IC (DCIC), suggesting that the mouse midbrain is more similar to that of other mammals than previously thought. We found that the DCIC comprises a thin sheet of neurons, sometimes extending barely 100 μm below the pial surface. The sound frequency representation in the DCIC approximated the mouse’s full hearing range, whereas dorsal CNIC neurons almost exclusively preferred low frequencies. The response properties of neurons in these two regions were otherwise surprisingly similar, and the frequency tuning of DCIC neurons was only slightly broader than that of CNIC neurons. In several animals, frequency gradients were observed in the DCIC, and a comparable tonotopic arrangement was observed across the boutons of the corticocollicular axons, which form a dense mesh beneath the dorsal surface of the IC. Nevertheless, acoustically responsive corticocollicular boutons were sparse, produced unreliable responses, and were more broadly tuned than DCIC neurons, suggesting that they have a largely modulatory rather than driving influence on auditory midbrain neurons.

The Journal of Neuroscience, August 5, 2015 • 35(31):10927–10939

Interspike Intervals Reveal Functionally Distinct Cell Populations in the Medial Entorhinal Cortex

Patrick Latuske, Oana Toader, and Kevin Allen

Department of Clinical Neurobiology, Medical Faculty of Heidelberg University and German Cancer Research Center (Deutsches Krebsforschungszentrum), 69120 Heidelberg, Germany

The superficial layers of the medial entorhinal cortex (MEC) contain spatially selective neurons that are crucial for spatial navigation and memory. These highly specialized neurons include grid cells, border cells, head-direction cells, and irregular spatially selective cells. In addition, MEC neurons display a large variability in their spike patterns at a millisecond time scale. In this study, we analyzed spike trains of neurons in the MEC superficial layers of mice and found that these neurons can be classified into two groups based on their propensity to fire spike doublets at 125–250 Hz. The two groups, labeled “bursty” and “non-bursty” neurons, differed in their spike waveforms and interspike interval adaptation but displayed a similar mean firing rate. Grid cell spatial periodicity was more commonly observed in bursty than in non-bursty neurons. In contrast, most neurons with head-direction selectivity or those that fired at the border of the environment were non-bursty neurons. During theta oscillations, both bursty and non-bursty neurons fired preferentially near the end of the descending phase of the cycle, but the spikes of bursty neurons occurred at an earlier phase than those of non-bursty neurons. Finally, analysis of spike-time crosscorrelations between simultaneously recorded neurons suggested that the two cell classes are differentially coupled to fast-spiking interneurons: bursty neurons were twice as likely to have excitatory interactions with putative interneurons as non-bursty neurons. These results demonstrate that bursty and non-bursty neurons are differentially integrated in the MEC network and preferentially encode distinct spatial signals.

The Journal of Neuroscience, August 5, 2015 • 35(31):10963–10976
**Functional Connectivity of Insula, Basal Ganglia, and Prefrontal Executive Control Networks during Hypoglycemia in Type 1 Diabetes**

Nicolas R. Bolo,¹,²,* Gail Musen,²,³,* Donald C. Simonson,²,⁴ Lisa D. Nickerson,¹,² Veronica L. Flores,¹ Tamar Siracusa,¹ Brandon Hager,¹ In Kyoon Lyoo,⁴ Perry F. Renshaw,¹,² and Alan M. Jacobson¹,²,³,⁵

¹Brain Imaging Center, McLean Hospital, Belmont, Massachusetts 02478, ²Harvard Medical School, Boston, Massachusetts 02115, ³Research Division, Joslin Diabetes Center, Boston, Massachusetts 02215, ⁴Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women’s Hospital, Boston, Massachusetts 02115, ⁵Department of Psychiatry, Beth Israel Deaconess Medical Center, Boston, Massachusetts 02215, ⁶Ewha Brain Institute and Graduate School of Pharmaceutical Sciences, Ewha Womans University, Seoul 120-750, South Korea, and ⁷Research Institute, Winthrop University Hospital, Mineola, New York 11501

Human brain networks mediating interoceptive, behavioral, and cognitive aspects of glycemic control are not well studied. Using group independent component analysis with dual-regression approach of functional magnetic resonance imaging data, we examined the functional connectivity changes of large-scale resting state networks during sequential euglycemic– hypoglycemic clamp studies in patients with type 1 diabetes and nondiabetic controls and how these changes during hypoglycemia were related to symptoms of hypoglycemia awareness and to concurrent glycylated hemoglobin (Hba1c) levels. During hypoglycemia, diabetic patients showed increased functional connectivity of the right anterior insula and the prefrontal cortex within the executive control network, which was associated with higher Hba1c. Controls showed decreased functional connectivity of the right anterior insula with the cerebellum/basal ganglia network and of temporal regions within the temporal pole network and increased functional connectivity in the default mode and sensorimotor networks. Functional connectivity reductions in the right basal ganglia were correlated with increases of self-reported hypoglycemic symptoms in controls but not in patients. Resting state networks that showed different group functional connectivity during hypoglycemia may be most sensitive to glycemic environment, and their connectivity patterns may have adapted to repeated glycemic excursions present in type 1 diabetes. Our results suggest that basal ganglia and insula mediation of interoceptive awareness during hypoglycemia is altered in type 1 diabetes. These changes could be neuroplastic adaptations to frequent hypoglycemic experiences. Functional connectivity changes in the insula and prefrontal cognitive networks could also reflect an adaptation to changes in brain metabolic pathways associated with chronic hyperglycemia.

The Journal of Neuroscience, August 5, 2015 • 35(31):11012–11023

---

**Synaptic Basis for Differential Orientation Selectivity between Complex and Simple Cells in Mouse Visual Cortex**

Ya-tang Li,¹,⁴ Bao-hua Liu,¹ Xiao-lin Chou,¹,⁴ Li I. Zhang,¹,³ and Huizhong W. Tao¹,²

¹Zilkha Neurogenetic Institute, ²Department of Cell and Neurobiology, ³Department of Physiology and Biophysics, and ⁴Graduate Programs, Keck School of Medicine, University of Southern California, Los Angeles, California 90033

In the primary visual cortex (V1), orientation-selective neurons can be categorized into simple and complex cells primarily based on their receptive field (RF) structures. In mouse V1, although previous studies have examined the excitatory/inhibitory interplay underlying orientation selectivity (OS) of simple cells, the synaptic bases for that of complex cells have remained obscure. Here, by combining in vivo loose-patch and whole-cell recordings, we found that complex cells, identified by their overlapping on/off subfields, had significantly weaker OS than simple cells at both spiking and subthreshold membrane potential response levels. Voltage-clamp recordings further revealed that although excitatory inputs to complex and simple cells exhibited a similar degree of OS, inhibition in complex cells was more narrowly tuned than excitation, whereas in simple cells inhibition was more broadly tuned than excitation. The differential inhibitory tuning can primarily account for the difference in OS between complex and simple cells. Interestingly, the differential synaptic tuning correlated well with the spatial organization of synaptic input: the inhibitory visual RF in complex cells was more elongated in shape than its excitatory counterpart and also was more elongated than that in simple cells. Together, our results demonstrate that OS of complex and simple cells is differentially shaped by cortical inhibition based on its orientation tuning profile relative to excitation, which is contributed at least partially by the spatial organization of RFs of presynaptic inhibitory neurons.

The Journal of Neuroscience, August 5, 2015 • 35(31):11081–11093

---

**Glutamate Receptors in the Central Nucleus of the Amygdala Mediate Cisplatin-Induced Malaise and Energy Balance Dysregulation through Direct Hindbrain Projections**

Amber L. Alhadeff,¹ Ruby A. Holland,² Alexandra Nelson,² Harvey J. Grill,¹ and Bart C. De Jonghe²

¹Department of Psychology and ²Department of Biobehavioral Health Sciences, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Cisplatin chemotherapy is used commonly to treat a variety of cancers despite severe side effects such as nausea, vomiting, and anorexia that compromise quality of life and limit treatment adherence. The neural mechanisms mediating these side effects remain elusive despite decades of clinical use. Recent data highlight the dorsal vagal complex (DVC), lateral parabrachial nucleus (IPBN), and central nucleus of the amygdala (CeA) as potential sites of action in mediating the side effects of cisplatin. Here, results from immunohistochemical studies in rats identified a population of cisplatin-activated DVC neurons that project to the IPBN and a population of cisplatin-activated IPBN calcitonin gene-related peptide (CGRP, a marker for glutamatergic neurons in the IPBN) neurons that project to the CeA, outlining a neuroanatomical circuit that is activated by cisplatin. CeA gene expressions of AMPA and NMDA glutamate receptor subunits were markedly increased after cisplatin treatment, suggesting that CeA glutamate receptor signaling plays a role in mediating cisplatin side effects. Consistent with gene expression results, behavioral/pharmacological data showed that CeA AMPA/kainate receptor blockade attenuates cisplatin-induced pica (a proxy for nausea/behavioral malaise in nonvomiting laboratory rodents) and that CeA NMDA receptor blockade attenuates cisplatin-induced anorexia and body weight loss in addition to pica, demonstrating that glutamate receptor signaling in the CeA is critical for...
the energy balance dysregulation caused by cisplatin treatment. Together, these data highlight a novel circuit and CGRP/glutamatergic mechanism through which cisplatin-induced malaise and energy balance dysregulation are mediated.

The Journal of Neuroscience, August 5, 2015 • 35(31):10940 –10948

**BEHAVIORAL/COGNITIVE**

### Neural Signature...


**Opponent Identity Influences Value Learning in Simple Games**

Timothy J. Vickery, 1 Matthew R. Kleinman, 2 Marvin M. Chun, 2,3,4 and Daeyeol Lee 2,3,4

1Department of Psychological and Brain Sciences, University of Delaware, Newark, Delaware 19716, 2Department of Neurobiology, 3Kavli Institute for Neuroscience, Yale University School of Medicine, New Haven, Connecticut 06510, and 4Department of Psychology, Yale University, New Haven, Connecticut 06520

Context plays a pivotal role in many decision-making scenarios, including social interactions wherein the identities and strategies of other decision makers often shape our behaviors. However, the neural mechanisms for tracking such contextual information are poorly understood. Here, we investigated how opponent identity affects human reinforcement learning during a simulated competitive game against two independent computerized opponents. We found that strategies of participants were affected preferentially by the outcomes of the previous interactions with the same opponent. In addition, reinforcement signals from the previous trial were less discriminable throughout the brain after the opponent changed, compared with when the same opponent was repeated. These opponent-selective reinforcement signals were particularly robust in right rostral anterior cingulate and right lingual regions, where opponent-selective reinforcement signals correlated with a behavioral measure of opponent-selective reinforcement learning. Therefore, when choices involve multiple contextual frames, such as different opponents in a game, decision making and its neural correlates are influenced by multithreaded histories of reinforcement. Overall, our findings are consistent with the availability of temporally overlapping, context-specific reinforcement signals.

The Journal of Neuroscience, August 5, 2015 • 35(31):11133–11143

**NEUROBIOLOGY OF DISEASE**

**Persistent Interneuronopathy in the Prefrontal Cortex of Young Adult Offspring Exposed to Ethanol In Utero**

Alexander G. J. Skorput, Vivek P. Gupta, Pamela W. L. Yeh, and Hermes H. Yeh

Department of Physiology and Neurobiology, Geisel School of Medicine at Dartmouth, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire 03756

Gestational exposure to ethanol has been reported to alter the disposition of tangentially migrating GABAergic cortical interneurons, but much remains to be elucidated. Here we first established the migration of interneurons as a proximal target of ethanol by limiting ethanol exposure in utero to the gestational window when tangential migration is at its height. We then asked whether the aberrant tangential migration of GABAergic interneurons persisted as an enduring interneuronopathy in the medial prefrontal cortex (mPFC) later in the life of offspring prenatally exposed to ethanol. Time pregnant mice with Nkx2.1Cre/Ai14 embryos harboring tdTomato-fluorescent medial ganglionic eminence (MGE)-derived cortical GABAergic interneurons were subjected to a 3 day binge-type 5% w/w ethanol consumption regimen from embryonic day (E) 13.5–16.5, spanning the peak of corticopetal interneuron migration in the fetal brain. Our binge-type regimen increased the density of MGE-derived interneurons in the E16.5 mPFC. In young adult offspring exposed to ethanol in utero, this effect persisted as an increase in the number of mPFC layer V parvalbumin-immunopositive interneurons. Commensurately, patch-clamp recording in mPFC layer V pyramidal neurons uncovered enhanced GABA-mediated spontaneous and evoked synaptic transmission, shifting the inhibitory/excitatory balance toward favoring inhibition. Furthermore, young adult offspring exposed to the 3 day binge-type ethanol regimen exhibited impaired reversal learning in a modified Barnes maze, indicative of decreased PFC-dependent behavioral flexibility, and heightened locomotor activity in an open field arena. Our findings underscore that aberrant neuronal migration, inhibitory/excitatory imbalance, and thus interneuronopathy contribute to indelible abnormal cortical circuit form and function in fetal alcohol spectrum disorders.

The Journal of Neuroscience, August 5, 2015 • 35(31):10977–10988

**The Effect of Body Posture on Brain Glymphatic Transport**

Hedok Lee, 1,2,* Lulu Xie, 5,* Mei Yu, 1 Hongyi Kang, 1 Tian Feng, 3 Rashid Deane, 3 Jean Logan, 4 Maiken Nedergaard, 5 and Helene Benveniste 1,2

1Department of Anesthesiology, 2Department of Radiology, and 3Department of Applied Mathematics and Statistics, Stony Brook University, Stony Brook, New York 11794, 4Department of Radiology, New York University Langone Medical Center, New York, New York 10016, and 5Center for Translational Neuromedicine, University of Rochester, Rochester, New York 14627

The glymphatic pathway expedites clearance of waste, including soluble amyloid β (Aβ) from the brain. Transport through this pathway is controlled by the brain’s arousal level because, during sleep or anesthesia, the brain’s interstitial space volume expands (compared with wakefulness), resulting in faster waste removal. Humans, as well as animals, exhibit different body postures during sleep, which may also affect waste removal. Therefore, not only the level of consciousness, but also body posture, might affect CSF-interstitial fluid (ISF) exchange efficiency. We used dynamic-contrast-enhanced MRI and kinetic modeling to quantify CSF-ISF exchange rates in anesthetized rodents’ brains in supine, prone, or lateral positions. To validate the MRI data and to assess specifically the influence of body posture on clearance of Aβ, we used fluorescence microscopy and radioactive tracers, respectively. The analysis showed that glymphatic transport was most efficient in the lateral position compared with the supine or prone positions. In the prone position, in which the rat’s head was in the most upright position (minimizing posture during the awake state), transport was characterized by “retention” of the tracer, slower clearance, and more CSF efflux along larger caliber cervical vessels. The optical imaging and radiotracer studies confirmed that glymphatic transport and Aβ clearance were superior in the lateral and supine positions. We propose that the most popular sleep posture (lateral) has evolved to optimize waste removal during sleep and that posture must be considered in diagnostic imaging procedures developed in the future to assess CSF-ISF transport in humans.

The Journal of Neuroscience, August 5, 2015 • 35(31):11034–11044