

This Week in The Journal

● Cellular/Molecular

Targeting Arc to Synaptic Sites

Fen Huang, Jennifer K. Chotiner, and Oswald Steward

(see pages 9054–9067)

Arc/Arg 3.1 is not only an immediate early gene, but its mRNA is also targeted to dendrites. Thus it has become a focus of studies linking neural activity to changes in synaptic efficacy. This week, Huang et al. further explored the signaling cascade involved in the targeting of Arc mRNA and protein to active synaptic sites. The authors induced long-term potentiation in adult anesthetized rats by stimulating the medial perforant path and recording the response in the dentate gyrus. High-frequency stimulation was continued for periods of up to 90 min. Polymerized actin, measured by phalloidin staining, colocalized with Arc/Arg 3.1 mRNA in the activated dendritic lamina within the molecular layer of the dentate gyrus. This colocalization was blocked by inhibition of Rho kinase or inhibition of actin polymerization with latrunculin B. ERK1 phosphorylation induced by high-frequency stimulation was also required for the targeting of Arc/Arg 3.1 mRNA.

▲ Development/Plasticity/Repair

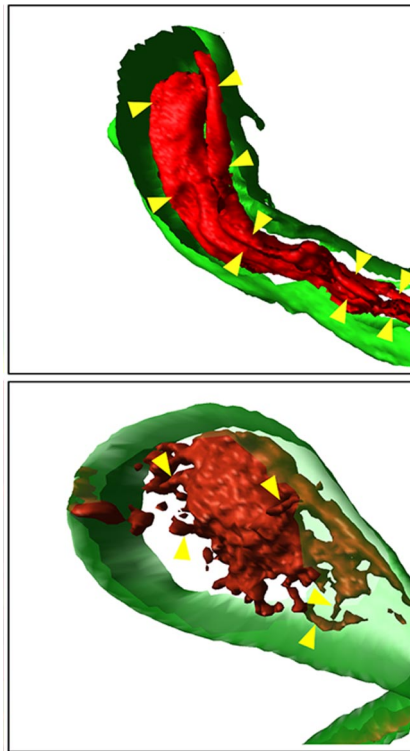
Retraction Bulbs and Microtubule Networks

Ali Ertürk, Farida Hellal, Joana Enes, and Frank Bradke

(see pages 9169–9180)

It's not altogether clear why injured peripheral axons can regenerate relatively easily, whereas central axons have a much rougher time. This week, Ertürk et al. decided to take a comparative look at microtubules in the business end of the axon: the tip or growth cone. Rather than growth cones, injured central axons have swellings at their tips called retraction bulbs that are the hallmark of a failed growth response. The authors lesioned the dorsal column or the sciatic nerve in 2- to 3-month-old mice and tracked axon tips with a fluorescent reporter. In central axons, retraction bulbs continue to in-

crease in size after injury and contained disorganized microtubule networks compared with the sleek and organized regenerating peripheral axons. Disruption of microtubules with nocodazole caused retraction bulb formation in peripheral axons *in vivo* and in cell culture. In contrast, stabilizing microtubules with taxol prevented retraction bulbs.



A three-dimensional reconstruction of microtubule networks in a growth cone (top) and a retraction bulb (bottom). The yellow arrowheads point to the parallel microtubule bundles in the growth cone compared with the dispersed microtubules in the retraction bulb. See the article by Ertürk et al. for details.

■ Behavioral/Systems/Cognitive

Mapping Fingerpads in S1 with Positive BOLD

Li M. Chen, Gregory H. Turner, Robert M. Friedman, Na Zhang, John C. Gore, Anna W. Roe, and Malcolm J. Avison

(see pages 9181–9191)

Blood oxygenation level-dependent (BOLD) functional magnetic resonance

imaging (fMRI) has been widely used to map functional brain activity in humans, whereas optical imaging of intrinsic signals (OIS) has been used for similar purposes in animals. Most BOLD studies use the “positive” signal, rather than the much smaller early negative BOLD that likely corresponds to the signal detected by OIS. OIS is generally regarded as having higher spatial resolution on the order of 100 μm and higher time resolution on the order of 100 ms. This week, Chen et al. compared the two techniques by mapping single distal fingerpad activation in the somatosensory cortex (S1) of anesthetized squirrel monkeys. Using a 9.4 T magnet, the authors report that positive BOLD signals without contrast agents could resolve submillimeter shifts in activation in area 3b, similar to what was detectable with OIS. Coregistration of fMRI and OIS maps in the same monkeys showed close agreement.

◆ Neurobiology of Disease

The Time Course of the Phenotype in HD Mice

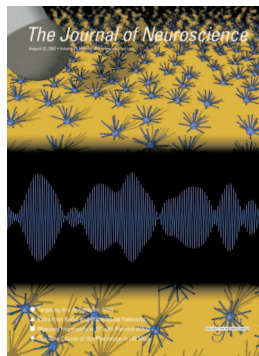
Mary Y. Heng, Sara J. Tallaksen-Greene, Peter J. Detloff, and Roger L. Albin

(see pages 8989–8998)

The long latency, measured in decades, before onset of symptoms is a hallmark of adult-onset Huntington's disease (HD). Yet putative treatments would best be tested before overt clinical symptoms emerge in man or in mouse models of the human disease. This week, Heng et al. tracked the time course of changes in behavior and in the striatum of the Hdh^(CAG150) knock-in mouse model of HD. All mice survived to 100 weeks, but by that point, they had a tremor, unsteady movements, and a staggering gait. A battery of behavioral tests revealed motor abnormalities at 70 and 100 weeks. There were also losses in striatal dopamine D1 and D2 receptors at 70 and 100 weeks and a loss of striatal neuron number at 100 weeks. These longitudinal studies not only validate this mouse model as exhibiting features consistent with HD but also provide a benchmark for its use in studies of pathogenesis and treatment.

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Cover legend: Peripheral waves are stereotyped olfactory responses that have been assumed to represent the synchronous activity of olfactory receptor neurons. In this issue, Díaz et al. show that peripheral waves can instead be explained as the addition of random-phase oscillators generating an interference pattern known as Rayleigh fading. The sketch depicts a metal electrode approaching the surface of the vertebrate olfactory epithelium, whereas the trace illustrates the characteristic modulation pattern shared by peripheral waves and Rayleigh fading. For more information, see the article by Díaz et al. in this issue (pages 9238–9245).

i This Week in The Journal

Brief Communications

- 9141 **To Do or Not to Do: The Neural Signature of Self-Control**
Marcel Brass and Patrick Haggard
- 9233 **Human 5-HT Transporter Availability Predicts Amygdala Reactivity *In Vivo***
Rebecca A. Rhodes, Naga Venkatesha Murthy, M. Alex Dresner, Sudhakar Selvaraj, Nikolaos Stavrakakis, Syed Babar, Philip J. Cowen, and Paul M. Grasby

Articles

CELLULAR MOLECULAR

- 8999 **Dendritic Spikes in Apical Dendrites of Neocortical Layer 2/3 Pyramidal Neurons**
Matthew Evan Larkum, Jack Waters, Bert Sakmann, and Fritjof Helmchen
- 9022 **Activation of Presynaptic GABA_A Receptors Induces Glutamate Release from Parallel Fiber Synapses**
Brandon M. Stell, Philippe Rostaing, Antoine Triller, and Alain Marty
- 9054 **Actin Polymerization and ERK Phosphorylation Are Required for Arc/Arg3.1 mRNA Targeting to Activated Synaptic Sites on Dendrites**
Fen Huang, Jennifer K. Chotiner, and Oswald Steward
- 9086 **Ca²⁺/Calmodulin Regulates Trafficking of Ca_v1.2 Ca²⁺ Channels in Cultured Hippocampal Neurons**
Hong-Gang Wang, Meena S. George, James Kim, Chaojian Wang, and Geoffrey S. Pitt
- 9146 **The Inhibition Site on Myelin-Associated Glycoprotein Is within Ig-Domain 5 and Is Distinct from the Sialic Acid Binding Site**
Zixuan Cao, Jin Qiu, Marco Domeniconi, Jianwei Hou, J. Barney Bryson, Wilfredo Mellado, and Marie T. Filbin
- 9192 **Excitatory Synaptic Transmission Persists Independently of the Glutamate–Glutamine Cycle**
Kaiwen Kam and Roger Nicoll
- 9238 **Amplitude Modulation Patterns of Local Field Potentials Reveal Asynchronous Neuronal Populations**
Javier Díaz, Pablo Razeto-Barry, Juan-Carlos Letelier, John Caprio, and Juan Bacigalupo

DEVELOPMENT/PLASTICITY/REPAIR

- 9094 **Requirement for Slit-1 and Robo-2 in Zonal Segregation of Olfactory Sensory Neuron Axons in the Main Olfactory Bulb**
Jin Hyung Cho, Manon Lépine, William Andrews, John Parnavelas, and Jean-François Cloutier
- 9130 **GABA_A Receptor-Mediated Signaling Alters the Structure of Spontaneous Activity in the Developing Retina**
Chih-Tien Wang, Aaron G. Blankenship, Anastasia Anishchenko, Justin Elstrott, Michael Fikhman, Shigetada Nakanishi, and Marla B. Feller
- 9169 **Disorganized Microtubules Underlie the Formation of Retraction Bulbs and the Failure of Axonal Regeneration**
Ali Ertürk, Farida Hellal, Joana Enes, and Frank Bradke

BEHAVIORAL/SYSTEMS/COGNITIVE

- 8979 **Functional Organization of Presynaptic Metabotropic Glutamate Receptors in Vagal Brainstem Circuits**
Kirsteen N. Browning and R. Alberto Travaglini
- 9068 **Astroglial Glutamate–Glutamine Shuttle Is Involved in Central Sensitization of Nociceptive Neurons in Rat Medullary Dorsal Horn**
Chen-Yu Chiang, Jing Wang, Yu-Feng Xie, Sun Zhang, James W. Hu, Jonathan O. Dostrovsky, and Barry J. Sessle
- 9077 **Metabotropic Glutamate 2/3 Receptors in the Ventral Tegmental Area and the Nucleus Accumbens Shell Are Involved in Behaviors Relating to Nicotine Dependence**
Matthias E. Liechti, Loïc Lhuillier, Klemens Kaupmann, and Athina Markou
- 9105 **Odorant Category Profile Selectivity of Olfactory Cortex Neurons**
Ikue Yoshida and Kensaku Mori
- 9181 **High-Resolution Maps of Real and Illusory Tactile Activation in Primary Somatosensory Cortex in Individual Monkeys with Functional Magnetic Resonance Imaging and Optical Imaging**
Li M. Chen, Gregory H. Turner, Robert M. Friedman, Na Zhang, John C. Gore, Anna W. Roe, and Malcolm J. Avison

NEUROBIOLOGY OF DISEASE

- 8989 **Longitudinal Evaluation of the *Hdh*^{(CAG)¹⁵⁰} Knock-In Murine Model of Huntington's Disease**
Mary Y. Heng, Sara J. Tallaksen-Greene, Peter J. Detloff, and Roger L. Albin
- 9009 **Sulfatide Storage in Neurons Causes Hyperexcitability and Axonal Degeneration in a Mouse Model of Metachromatic Leukodystrophy**
Matthias Eckhardt, Kerstin Khalaj Hedayati, Julika Pitsch, Renate Lüllmann-Rauch, Heinz Beck, Simon Ngamli Fewou, and Volkmar Gieselmann
- 9032 **Angiotensin II Controls Occludin Function and Is Required for Blood–Brain Barrier Maintenance: Relevance to Multiple Sclerosis**
Karolina Wosik, Romain Cayrol, Aurore Dodelet-Devillers, France Berthelet, Monique Bernard, Robert Mouldjian, Alain Bouthillier, Timothy L. Reudelhuber, and Alexandre Prat
- 9043 **Dark Rearing Rescues P23H Rhodopsin-Induced Retinal Degeneration in a Transgenic *Xenopus laevis* Model of Retinitis Pigmentosa: A Chromophore-Dependent Mechanism Characterized by Production of N-Terminally Truncated Mutant Rhodopsin**
Beatrice M. Tam and Orson L. Moritz

- 9115 Immunotherapy Targeting Pathological Tau Conformers in a Tangle Mouse Model Reduces Brain Pathology with Associated Functional Improvements**
Ayodeji A. Asuni, Allal Boutajangout, David Quartermain, and Einar M. Sigurdsson
- 9155 The Tau N279K Exon 10 Splicing Mutation Recapitulates Frontotemporal Dementia and Parkinsonism Linked to Chromosome 17 Tauopathy in a Mouse Model**
Hana N. Dawson, Viviana Cantillana, Liling Chen, and Michael P. Vitek
- 9201 Microarray Analysis of the Cellular Pathways Involved in the Adaptation to and Progression of Motor Neuron Injury in the SOD1 G93A Mouse Model of Familial ALS**
Laura Ferraiuolo, Paul R. Heath, Hazel Holden, Paul Kasher, Janine Kirby, and Pamela J. Shaw
- 9220 Different Species of α -Synuclein Oligomers Induce Calcium Influx and Seeding**
Karin M. Danzer, Dorothea Haasen, Anne R. Karow, Simon Moussaud, Matthias Habeck, Armin Giese, Hans Kretschmar, Bastian Hengerer, and Marcus Kostka

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To Do or Not to Do: The Neural Signature of Self-Control

Marcel Brass^{1,2} and Patrick Haggard³

¹Max Planck Institute for Human Cognitive and Brain Sciences, 04103 Leipzig, Germany, ²Department of Experimental Psychology, Ghent University, 9000 Ghent, Belgium, and ³Institute of Cognitive Neuroscience and Department of Psychology, University College London, London WC1N 3AR, United Kingdom

Voluntary action is fundamental to human existence. Recent research suggests that volition involves a specific network of brain activity, centered on the fronto-medial cortex. An important but neglected aspect of intentional action involves the decision whether to act or not. This decision process is crucial in daily life because it allows us to form intentions without necessarily implementing them. In the present study, we investigate the neural correlates of intentionally inhibiting actions using functional magnetic resonance imaging. Our data show that a specific area of the fronto-medial cortex is more strongly activated when people prepare manual actions but then intentionally cancel them, compared with when they prepare and then complete the same actions. Our results suggest that the human brain network for intentional action includes a control structure for self-initiated inhibition or withholding of intended actions. The mental control of action has an enduring scientific interest, linked to the philosophical concept of “free will.” Our results identify a candidate brain area that reflects the crucial decision to do or not to do.

The Journal of Neuroscience, August 22, 2007 • 27(34):9141–9145

Human 5-HT Transporter Availability Predicts Amygdala Reactivity *In Vivo*

Rebecca A. Rhodes,¹ Naga Venkatesha Murthy,^{1,3} M. Alex Dresner,² Sudhakar Selvaraj,^{1,4} Nikolaos Stavrakakis,¹ Syed Babar,⁵ Philip J. Cowen,⁴ and Paul M. Grasby¹

¹Psychiatry Group, ²Imaging Sciences Department, Medical Research Council (MRC) Clinical Sciences Centre, and ³Experimental Medicine, Psychiatry Clinical Pharmacology Discovery Medicine, GlaxoSmithKline Clinical Imaging Centre, Imperial College London, London W12 0NN, United Kingdom, ⁴Department of Psychiatry, University of Oxford, Oxford OX3 7JX, United Kingdom, and ⁵Radiology Department, Hammersmith Hospital, London W12 0HS, United Kingdom

The amygdala plays a central role in fear conditioning, emotional processing, and memory modulation. A postulated key component of the neurochemical regulation of amygdala function is the neurotransmitter 5-hydroxytryptamine (5-HT), and synaptic levels of 5-HT in the amygdala and elsewhere are critically regulated by the 5-HT transporter (5-HTT). The aim of this study was to directly examine the relationship between 5-HTT availability and amygdala activity using multimodal [positron emission tomography (PET) and functional magnetic resonance imaging (fMRI)] imaging measures in the same individuals. Healthy male volunteers who had previously undergone an [¹¹C]-3-amino-4-(2-dimethylaminomethylphenylsulfanyl)-benzonitrile ([¹¹C]-DASB) PET scan to determine 5-HTT availability completed an fMRI emotion recognition task. [¹¹C]-DASB binding potential values were calculated for the amygdala using arterial input function and linear graphical (Logan) analysis. fMRI was performed on a 3T Philips Intera scanner, and data were analyzed using SPM2 (Wellcome Department Imaging Neuroscience, University College London). Percentage signal change during the task was extracted from the amygdala using MarsBaR (Brett et al., 2002). fMRI analysis revealed significant amygdala activation during the emotion recognition task. Region of interest analyses demonstrated a significant negative correlation between fMRI signal change in the left amygdala and 5-HTT availability in the left amygdala, with 5-HTT availability accounting for ~42% of the variability in left amygdala activity. Our novel *in vivo* data highlight the central importance of the serotonergic system in the responsiveness of the human amygdala during emotional processing.

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Articles

CELLULAR/MOLECULAR

Dendritic Spikes in Apical Dendrites of Neocortical Layer 2/3 Pyramidal Neurons

Matthew Evan Larkum, Jack Waters, Bert Sakmann, and Fritjof Helmchen

Abteilung Zellphysiologie, Max-Planck-Institut für Medizinische Forschung, D-69120 Heidelberg, Germany

Layer 2/3 (L2/3) pyramidal neurons are the most abundant cells of the neocortex. Despite their key position in the cortical microcircuit, synaptic integration in dendrites of L2/3 neurons is far less understood than in L5 pyramidal cell dendrites, mainly because of the difficulties in obtaining electrical recordings from thin dendrites. Here we directly measured passive and active properties of the apical dendrites of L2/3 neurons in rat brain slices using dual dendritic–somatic patch-clamp recordings and calcium imaging. Unlike L5 cells, L2/3 dendrites displayed little sag in response to long current pulses, which suggests a low density of I_h in the dendrites and soma. This was also consistent with a slight increase in input resistance with distance from the soma. Brief current injections into the apical dendrite evoked relatively short (half-width 2–4 ms) dendritic spikes that were isolated from the soma for near-threshold currents at sites beyond the middle of the apical dendrite. Regenerative dendritic potentials and large concomitant calcium transients were also elicited by trains of somatic action potentials (APs) above a critical frequency (130 Hz), which was slightly higher than in L5 neurons. Initiation of dendritic spikes was facilitated by backpropagating somatic APs and could cause an additional AP at the soma. As in L5 neurons, we found that distal dendritic calcium transients are sensitive to a long-lasting block by GABAergic inhibition. We conclude that L2/3 pyramidal neurons can generate dendritic spikes, sharing with L5 pyramidal neurons fundamental properties of dendritic excitability and control by inhibition.

The Journal of Neuroscience, August 22, 2007 • 27(34):8999–9008

Activation of Presynaptic GABA_A Receptors Induces Glutamate Release from Parallel Fiber Synapses

Brandon M. Stell,¹ Philippe Rostaing,² Antoine Triller,² and Alain Marty¹

¹Laboratoire de Physiologie Cérébrale, Unité de Formation et de Recherche Biomédicale, Université Paris Descartes, 75006 Paris, France, and ²Inserm, Unité 789, Ecole Normale Supérieure, 75005 Paris, France

The parallel fibers relay information coming into the cerebellar cortex from the mossy fibers, and they form synapses with molecular layer interneurons (MLIs) and Purkinje cells. Here we show that activation of ionotropic GABA receptors (GABA_ARs) induces glutamate release from parallel fibers onto both MLIs and Purkinje cells. These GABA-induced EPSCs have kinetics and amplitudes identical to random spontaneous currents (sEPSCs), but, unlike sEPSCs, they occur in bursts of between one and five successive events. The variation in amplitude of events within bursts is significantly less than the variation of all sEPSC amplitudes, suggesting that the bursts result from repetitive activation of single presynaptic fibers. Electron microscopy of immunogold-labeled α -1 subunits revealed GABA_ARs on parallel fiber terminals. We suggest that the activation of these receptors underlies the increased amplitude of parallel fiber-evoked Purkinje cell EPSCs seen with application of exogenous GABA or after the release of GABA from local interneurons. These results occur only when molecular layer GABA_ARs are activated, and the effects are abolished when the receptors are blocked by the GABA_AR antagonist gabazine (5 μ M). From these data, we conclude that GABA_ARs located on parallel fibers depolarize parallel fiber terminals beyond the threshold for Na⁺ channel activation and thereby induce glutamate release onto MLIs and Purkinje cells.

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Actin Polymerization and ERK Phosphorylation Are Required for Arc/Arg3.1 mRNA Targeting to Activated Synaptic Sites on Dendrites

Fen Huang,¹ Jennifer K. Chotiner,¹ and Oswald Steward^{1,2,3}

Departments of ¹Anatomy and Neurobiology, ²Neurobiology and Behavior, and Neurosurgery, Reeve-Irvine Research Center, and ³Center for the Neurobiology of Learning and Memory, University of California at Irvine, Irvine, California 92697

The mRNA for the immediate early gene *Arc/Arg3.1* is induced by strong synaptic activation and is rapidly transported into dendrites, where it localizes at active synaptic sites. NMDA receptor activation is critical for mRNA localization at active synapses, but downstream events that mediate localization are not known. The patterns of synaptic activity that induce mRNA localization also trigger a dramatic polymerization of actin in the activated dendritic lamina and phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2) throughout the postsynaptic cytoplasm. The local polymerization of actin in the activated dendritic lamina is of particular interest because it occurs in the same dendritic domains in which newly synthesized *Arc/Arg3.1* mRNA localizes. Here, we explore the role of activity-induced alterations in the actin network and mitogen-activated protein (MAP) kinase activation in *Arc/Arg3.1* mRNA localization. We show that actin polymerization induced by high-frequency stimulation is blocked by local inhibition of Rho kinase, and *Arc/Arg3.1* mRNA localization is abrogated in the region of Rho kinase blockade. Local application of latrunculin B, which binds to actin monomers and inhibits actin polymerization, also blocked the targeting of *Arc/Arg3.1* mRNA to activated synaptic sites. Local application of the MAP kinase inhibitor U0126 (1,4-diamino-2,3-dicyano-1,4-bis[2-amino-phenylthio]butadiene) blocked ERK phosphorylation, and also blocked *Arc/Arg3.1* mRNA localization. Our results indicate that the reorganization of the actin cytoskeletal network in conjunction with MAP kinase activation is required for targeting newly synthesized *Arc/Arg3.1* mRNA to activated synaptic sites.

The Journal of Neuroscience, August 22, 2007 • 27(34):9054–9067

Ca²⁺/Calmodulin Regulates Trafficking of Ca_v1.2 Ca²⁺ Channels in Cultured Hippocampal Neurons

Hong-Gang Wang,^{1*} Meena S. George,^{3*} James Kim,¹ Chaojian Wang,¹ and Geoffrey S. Pitt^{1,2}

Departments of ¹Pharmacology and ²Medicine, Division of Cardiology, ³Center for Neurobiology and Behavior, College of Physicians and Surgeons of Columbia University, New York, New York 10032

As the Ca²⁺-sensor for Ca²⁺-dependent inactivation, calmodulin (CaM) has been proposed, but never definitively demonstrated, to be a constitutive Ca_v1.2 Ca²⁺ channel subunit. Here we show that CaM is associated with the Ca_v1.2 pore-forming α_{1C} subunit in brain in a Ca²⁺-independent manner. Within its CaM binding pocket, α_{1C} has been proposed to contain a membrane targeting domain. Because ion channel subunits assemble early during channel biosynthesis, we postulated that this association with CaM could afford the opportunity for Ca²⁺-dependent regulation of membrane targeting. We showed that the isolated domain functioned as a Ca²⁺/CaM regulated trafficking determinant for CD8 (a model transmembrane protein) using fluorescent-activated cell sorting analysis and, using green fluorescent protein-tagged α_{1C} subunits expressed in cultured hippocampal neurons, that Ca²⁺/CaM interaction with this domain accelerated trafficking of Ca_v1.2 channels to distal regions of the dendritic arbor. Furthermore, this Ca²⁺/CaM-accelerated trafficking was activity dependent. Thus, CaM imparts Ca²⁺-dependent regulation not only to mature Ca_v1.2 channels at the cell surface but also to steps during channel biosynthesis.

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The Inhibition Site on Myelin-Associated Glycoprotein Is within Ig-Domain 5 and Is Distinct from the Sialic Acid Binding Site

Zixuan Cao, Jin Qiu, Marco Domeniconi, Jianwei Hou, J. Barney Bryson, Wilfredo Mellado, and Marie T. Filbin

The Department of Biological Sciences, Hunter College, City University of New York, New York, New York 10021

Myelin-associated glycoprotein (MAG) is a potent inhibitor of axonal regeneration. It contains five Ig-like domains and is a sialic binding protein. Previously, we showed that the sialic acid binding site on MAG maps to arginine 118 in Ig domain 1 (Kelm et al., 1994). However, sialic acid binding was neither necessary nor sufficient for MAG to bring about inhibition of neurite outgrowth. Consistent with this, we now map a distinct inhibition site on MAG to Ig domain 5 (Ig-5). We show that when a truncated form of MAG missing Ig domains 1 and 2 is expressed by Chinese hamster ovary (CHO) cells, it does not bind sialic acid, but still inhibits neurite outgrowth almost as effectively as full-length MAG. To determine whether the inhibition site mapped to Ig-3, Ig-4, or Ig-5, we made chimeric molecules of various combinations of these three MAG Ig domains fused to Ig domains from another Ig family member, sialoadhesin (Sn), which also binds to sialic acid in the same linkage as MAG. The MAG-Sn molecules were expressed in CHO cells and all contained five Ig domains and were able to bind sialic acid. However, only the chimeric molecules containing MAG Ig-5 inhibited neurite outgrowth. Furthermore, peptides corresponding to sequences in MAG Ig-5, but not Ig-4 or Sn Ig-5, are able to block inhibition of neurite outgrowth by both wild-type MAG and CNS myelin. We conclude that the inhibition site on MAG is carried by Ig domain 5 and that this site is distinct from the sialic-acid binding site.

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Excitatory Synaptic Transmission Persists Independently of the Glutamate–Glutamine Cycle

Kaiwen Kam^{1,2,3} and Roger Nicoll^{1,2}

Departments of ¹Cellular and Molecular Pharmacology and ²Physiology, and ³Graduate Program in Neuroscience, University of California, San Francisco, San Francisco, California 94143-2140

The glutamate–glutamine cycle is thought to be integral in continuously replenishing the neurotransmitter pool of glutamate. Inhibiting glial transfer of glutamine to neurons leads to rapid impairment in physiological and behavioral function; however, the degree to which excitatory synaptic transmission relies on the normal operation of this cycle is unknown. In slices and cultured neurons from rat hippocampus, we enhanced the transfer of glutamine to neurons, a fundamental step in this cycle, by adding exogenous glutamine. Although raising glutamine augments synaptic transmission by increasing vesicular glutamate, access to this synthetic pathway by exogenously applied glutamine to neurons is delayed and slow, challenging mechanisms linking the rapid effects of pharmacological inhibitors to decreased vesicular glutamate. We find that pharmacological inhibitors of glutamine synthetase or system A transporters cause an acute depression of basal synaptic transmission that is rapidly reversible, which is unlikely to be attributable to the rapid loss of vesicular glutamate. Furthermore, release of vesicular glutamate remains robust even during the prolonged removal of glutamine from pure neuronal cultures. We conclude that neurons have the capacity to store or produce glutamate for long periods of time, independently of glia and the glutamate–glutamine cycle.

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Amplitude Modulation Patterns of Local Field Potentials Reveal Asynchronous Neuronal Populations

Javier Díaz,¹ Pablo Razeto-Barry,¹ Juan-Carlos Letelier,¹ John Caprio,³ and Juan Bacigalupo^{1,2}

¹Department of Biology, Faculty of Sciences, University of Chile, Santiago, Chile 7800023, and ²Institute of Cell Dynamics and Biotechnology, University of Chile, Santiago, Chile 8370456, and ³Department of Biological Sciences, Louisiana State University, Baton Rouge, Louisiana 70803

Neural oscillations, which appear in several areas of the nervous system and cover a wide frequency range, are a prominent issue in current neuroscience. Extracellularly recorded oscillations are generally thought to be a manifestation of a neural population with synchronized electrical activity resulting from coupling mechanisms. The vertebrate olfactory neuroepithelium exhibits β -band oscillations, termed peripheral waves (PWs), in their population response to odor stimulation. Here, we examine PWs in the channel catfish and propose that their properties could be explained as the superposition of asynchronous oscillators. Our model shows that the intriguing random pattern of amplitude-modulated PWs could be explained by Rayleigh fading, an interference phenomenon well known in physics and recognizable using statistical methods and signal analysis. We are proposing a mathematical fingerprint to characterize neural signals generated by the addition of random phase oscillators. Our interpretation of PWs as arising from asynchronous oscillators could be generalized to other neuronal populations, because it suggests that neural oscillations, detected in local field potential recordings within a narrow frequency band, do not necessarily originate from synchronization events.

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Requirement for Slit-1 and Robo-2 in Zonal Segregation of Olfactory Sensory Neuron Axons in the Main Olfactory Bulb

Jin Hyung Cho,^{1,2} Manon Lépine,^{1,2} William Andrews,³ John Parnavelas,³ and Jean-François Cloutier^{1,2}

¹Montreal Neurological Institute, Centre for Neuronal Survival, Montréal, Québec, Canada H3A 2B4, ²Department of Neurology and Neurosurgery, McGill University, Montréal, Québec, Canada H3A 2B4, and ³Medical Research Council Centre for Developmental Neurobiology, King's College London, London SE1 1UL, United Kingdom

The formation of precise stereotypic connections in sensory systems is critical for the ability to detect and process signals from the environment. In the olfactory system, olfactory sensory neurons (OSNs) project axons to spatially defined glomeruli within the olfactory bulb (OB). A spatial relationship exists between the location of OSNs within the olfactory epithelium (OE) and their glomerular targets along the dorsoventral axis in the OB. The molecular mechanisms underlying the zonal segregation of OSN axons along the dorsoventral axis of the OB are poorly understood. Using *robo-2*^{-/-} (roundabout) and *slit-1*^{-/-} mice, we examined the role of the Slit family of axon guidance cues in the targeting of OSN axons during development. We show that a subset of OSN axons that normally project to the dorsal region of the OB mistarget and form glomeruli in the ventral region in *robo-2*^{-/-} and *slit-1*^{-/-} mice. In addition, we show that the Slit receptor, Robo-2, is expressed in OSNs in a high dorsomedial to low ventrolateral gradient across the OE and that Slit-1 and Slit-3 are expressed in the ventral region of the OB. These results indicate that the dorsal-to-ventral segregation of OSN axons are not solely defined by the location of OSNs within the OE but also relies on axon guidance cues.

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GABA_A Receptor-Mediated Signaling Alters the Structure of Spontaneous Activity in the Developing Retina

Chih-Tien Wang,¹ Aaron G. Blankenship,^{1,2*} Anastasia Anishchenko,^{1*} Justin Elstrott,¹ Michael Fikhman,¹ Shigetada Nakanishi,^{3,4} and Marla B. Feller¹

¹Neurobiology Section, Division of Biological Sciences and ²Neurosciences Graduate Program, University of California, San Diego, La Jolla, California 92093, ³Osaka Bioscience Institute, Suita, Osaka 565-0874, Japan, and ⁴Department of Molecular and System Biology, Graduate School of Biostudies, Kyoto University, Kyoto 606-8501, Japan

Ambient GABA modulates firing patterns in adult neural circuits by tonically activating extrasynaptic GABA_A receptors. Here, we demonstrate that during a developmental period when activation of GABA_A receptors causes membrane depolarization, tonic activation of GABA_A receptors blocks all spontaneous activity recorded in retinal ganglion cells (RGCs) and starburst amacrine cells (SACs). Bath application of the GABA_A receptor agonist muscimol blocked spontaneous correlated increases in intracellular calcium concentration and compound postsynaptic currents in RGCs associated with retinal waves. In addition, GABA_A receptor agonists activated a tonic current in RGCs that significantly reduced their excitability. Using a transgenic mouse in which green fluorescent protein is expressed under the metabotropic glutamate receptor subtype 2 promoter to target recordings from SACs, we found that GABA_A receptor agonists blocked compound postsynaptic currents and also activated a tonic current. GABA_A receptor antagonists reduced the holding current in SACs but not RGCs, indicating that ambient levels of GABA tonically activate GABA_A receptors in SACs. GABA_A receptor antagonists did not block retinal waves but did alter the frequency and correlation structure of spontaneous RGC firing. Interestingly, the drug aminophylline, a general adenosine receptor antagonist used to block retinal waves, induced a tonic GABA_A receptor antagonist-sensitive current in outside-out patches excised from RGCs, indicating that aminophylline exerts its action on retinal waves by direct activation of GABA_A receptors. These findings have implications for how various neuroactive drugs and neurohormones known to modulate extrasynaptic GABA_A receptors may influence spontaneous firing patterns that are critical for the establishment of adult neural circuits.

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Disorganized Microtubules Underlie the Formation of Retraction Bulbs and the Failure of Axonal Regeneration

Ali Ertürk, Farida Hellal, Joana Enes, and Frank Bradke

Max-Planck Institute of Neurobiology, Axonal Growth and Regeneration, 82152 Martinsried, Germany

Axons in the CNS do not regrow after injury, whereas lesioned axons in the peripheral nervous system (PNS) regenerate. Lesioned CNS axons form characteristic swellings at their tips known as retraction bulbs, which are the nongrowing counterparts of growth cones. Although much progress has been made in identifying intracellular and molecular mechanisms that regulate growth cone locomotion and axonal elongation, a comprehensive understanding of how retraction bulbs form and why they are unable to grow is still elusive. Here we report the analysis of the morphological and intracellular responses of injured axons in the CNS compared with those in the PNS. We show that retraction bulbs of injured CNS axons increase in size over time, whereas growth cones of injured PNS axons remain constant. Retraction bulbs contain a disorganized microtubule network, whereas growth cones possess the typical bundling of microtubules. Using *in vivo* imaging, we find that pharmacological disruption of microtubules in growth cones transforms them into retraction bulb-like structures whose growth is inhibited. Correspondingly, microtubule destabilization of sensory neurons in cell culture induces retraction bulb formation. Conversely, microtubule stabilization prevents the formation of retraction bulbs and decreases axonal degeneration *in vivo*. Finally, microtubule stabilization enhances the growth capacity of CNS neurons cultured on myelin. Thus, the stability and organization of microtubules define the fate of

lesioned axonal stumps to become either advancing growth cones or nongrowing retraction bulbs. Our data pinpoint microtubules as a key regulatory target for axonal regeneration.

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BEHAVIORAL/SYSTEMS/COGNITIVE

Functional Organization of Presynaptic Metabotropic Glutamate Receptors in Vagal Brainstem Circuits

Kirsteen N. Browning and R. Alberto Travagli

Department of Neuroscience, Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, Louisiana 70808

We demonstrated previously that, by suppressing cAMP levels, metabotropic glutamate receptors (mGluRs) play a crucial role in opioid receptor trafficking on GABAergic nerve terminals within gastric brainstem vagal circuits. Using whole-cell patch-clamp recordings, we aimed to correlate the influence of sensory vagal afferent fibers with the functional organization of mGluRs on the synaptic connections between the nucleus tractus solitarius and dorsal motor nucleus of the vagus. Group II mGluRs were identified on both excitatory and inhibitory synapses; the receptor-selective agonist APDC [(2*R*,4*R*)-4-aminopyrrolidine-2,4-dicarboxylate] induced a concentration-dependent decrease in glutamatergic and GABAergic synaptic transmission (EC_{50} , $\sim 20 \mu M$ for both). The group II mGluRs were activated tonically on GABAergic, but not glutamatergic synapses, as the receptor-selective antagonist (2*S*)- α -ethylglutamic acid (EGLU; $200 \mu M$) modulated GABA currents only. After selective vagal deafferentation, EGLU was without effect, suggesting that vagal afferent (sensory) fibers are the source of this tonic input. Conversely, group III mGluRs, although not activated tonically, were present on excitatory, but not inhibitory, synapses; in fact, the receptor-selective agonist L-AP-4 [L-(+)-2-amino-4-phosphonbutyric acid] induced a concentration-dependent decrease in glutamatergic synaptic transmission (EC_{50} , $\sim 2 \mu M$) but had no effect on GABAergic synaptic transmission. Together with our previous results on receptor trafficking, these data suggest that visceral information plays a fundamental role in shaping the response of homeostatic brainstem circuits that receive inputs from higher integrative neuronal centers.

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Astroglial Glutamate–Glutamine Shuttle Is Involved in Central Sensitization of Nociceptive Neurons in Rat Medullary Dorsal Horn

Chen-Yu Chiang,^{1*} Jing Wang,^{1*} Yu-Feng Xie,¹ Sun Zhang,¹ James W. Hu,¹ Jonathan O. Dostrovsky,² and Barry J. Sessle^{1,2}

¹Faculty of Dentistry, University of Toronto, Toronto, Ontario, Canada M5G 1G6, and ²Department of Physiology, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada M5S 1A8

Growing evidence suggests that astroglia are involved in pain states, but no studies have tested their possible involvement in modulating the activity of nociceptive neurons per se. This study has demonstrated that the central sensitization induced in functionally identified nociceptive neurons in trigeminal subnucleus caudalis (the medullary dorsal horn) by application of an inflammatory irritant to the rat's tooth pulp can be significantly attenuated by continuous intrathecal superfusion of methionine sulfoximine (MSO; 0.1 mM), an inhibitor of the astroglial enzyme glutamine synthetase that is involved in the glutamate–glutamine shuttle. Simultaneous superfusion of MSO and glutamine (0.25 mM) restored the irritant-induced central sensitization. In control experiments, superfusion of either MSO or glutamine alone, or vehicle, did not produce any significant changes in neuronal properties. These findings suggest that the astroglial glutamate–glutamine shuttle is essential for the initiation of inflammation-induced central sensitization but that inhibition of astroglial function may not affect normal nociceptive processing.

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Metabotropic Glutamate 2/3 Receptors in the Ventral Tegmental Area and the Nucleus Accumbens Shell Are Involved in Behaviors Relating to Nicotine Dependence

Matthias E. Liechti,¹ Loic Lhuillier,² Klemens Kaupmann,² and Athina Markou¹

¹Department of Psychiatry, School of Medicine, University of California, San Diego, La Jolla, California 92093, and ²Neuroscience Research, Novartis Institutes for Biomedical Research, Novartis Pharma, CH-4002 Basel, Switzerland

The motivation to maintain nicotine self-administration and dependence may involve alterations in glutamatergic neurotransmission. Metabotropic glutamate (mGlu) 2/3 receptors regulate glutamate and dopamine release in the ventral tegmental area (VTA) and the nucleus accumbens (NAc) shell, two brain areas critically involved in reward and motivational processes. We found that acute systemic, as well as intra-VTA or intra-NAc, administration of the mGlu2/3 receptor agonist LY379268 [(–)-2-oxa-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylate] decreased nicotine, but not food, self-administration in rats. In addition, nicotine self-administration downregulated mGlu2/3 receptor function in corticolimbic rat brain sites including the VTA and the NAc, demonstrated by decreased coupling of mGlu2/3 receptors to G-proteins in the [³⁵S]GTP γ S binding assay. Furthermore, repeated treatment with LY379268 reduced nicotine self-administration at the beginning of a 14 d treatment period; however, the number of nicotine infusions earned gradually returned to baseline levels, indicating tolerance to the effects of repeated LY379268 treatment. Finally, LY379268 administration decreased both cue-induced reinstatement of nicotine- and food-seeking behavior. Together, these findings indicate an important role for mGlu2/3 receptors in the posterior VTA and the NAc shell in the mediation of the rewarding effects of nicotine and potentially in cue-induced nicotine-seeking behavior.

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Odorant Category Profile Selectivity of Olfactory Cortex Neurons

Ikue Yoshida and Kensaku Mori

Department of Physiology, Graduate School of Medicine, University of Tokyo, Bunkyo-ku, Tokyo 113-0033, Japan

The olfactory cortex receives converging axonal inputs from many mitral and tufted cells in the olfactory bulb. Recent studies indicate that single cortical neurons integrate signals from diverse odorants. However, there remains a basic question, namely, the signals from which kinds of odorants are integrated by the individual cortical neurons? The present study examined the possibility that some cortical neurons integrate signals from distinct component odorants of natural foods because individual foods produce a fixed combination of odorants. Previous psychophysical studies of core odorants emitted by fruits and vegetables suggest that the olfactory images of individual natural foods are basically characterized by the profile of structural and perceptual categories of food-born odorants. The single-unit spike responses of neurons in the dorsoposterior part of rat anterior piriform cortex to a panel of eight food-related categories of odorants were herein examined. The results showed that many cortical neurons in this region are tuned selectively to either a single category or a specific combination of distinct categories. The cortical neurons showed mixture facilitation and mixture inhibition when stimulated with mixtures of distinct categories, thus suggesting that olfactory circuits may play a role in enhancing the category-profile selectivity of individual neurons. These results indicate that signals from distinct categories of food-born odorants are integrated in these cortical neurons. This suggests that these cortical neurons detect the odorant-category profile of foods to distinguish distinct food odors.

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High-Resolution Maps of Real and Illusory Tactile Activation in Primary Somatosensory Cortex in Individual Monkeys with Functional Magnetic Resonance Imaging and Optical Imaging

Li M. Chen,^{1,2,3} Gregory H. Turner,¹ Robert M. Friedman,³ Na Zhang,^{1,5} John C. Gore,^{1,2,5,6,7} Anna W. Roe,³ and Malcolm J. Avison^{1,2,4}

¹Institute of Imaging Science and Departments of ²Radiology and Radiological Sciences, ³Psychology, ⁴Pharmacology, ⁵Physics and Astronomy,

⁶Biomedical Engineering, and ⁷Molecular Physiology and Biophysics, Vanderbilt University, Nashville, Tennessee 37232

Although blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI) has been widely used to explore human brain function, questions remain regarding the ultimate spatial resolution of positive BOLD fMRI, and indeed the extent to which functional maps revealed by positive BOLD correlate spatially with maps obtained with other high-spatial-resolution mapping techniques commonly used in animals, such as optical imaging of intrinsic signal (OIS) and single-unit electrophysiology. Here, we demonstrate that the positive BOLD signal at 9.4T can reveal the fine topography of individual fingerpads in single-condition activation maps in nonhuman primates. These digit maps are similar to maps obtained from the same animal using intrinsic optical imaging. Furthermore, BOLD fMRI reliably resolved submillimeter spatial shifts in activation in area 3b previously identified with OIS (Chen et al., 2003) as neural correlates of the “funneling illusion.” These data demonstrate that at high field, high-spatial-resolution topographic maps can be achieved using the positive BOLD signal, weakening previous notions regarding the spatial specificity of the positive BOLD signal.

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NEUROBIOLOGY OF DISEASE

Longitudinal Evaluation of the *Hdh*^{(CAG)¹⁵⁰} Knock-In Murine Model of Huntington’s Disease

Mary Y. Heng,^{1,2} Sara J. Tallaksen-Greene,² Peter J. Detloff,³ and Roger L. Albin^{1,2,4}

¹Neuroscience Graduate Program and ²Department of Neurology, University of Michigan, Ann Arbor, Michigan 48109, ³Department of Biochemistry and Molecular Genetics, University of Alabama at Birmingham, Birmingham, Alabama 36294, and ⁴Geriatrics Research, Education, and Clinical Center, Ann Arbor Veterans Administration Medical Center, Ann Arbor, Michigan 48105

Several murine genetic models of Huntington’s disease (HD) have been developed. Murine genetic models are crucial for identifying mechanisms of neurodegeneration in HD and for preclinical evaluation of possible therapies for HD. Longitudinal analysis of mutant phenotypes is necessary to validate models and to identify appropriate periods for analysis of early events in the pathogenesis of neurodegeneration. Here we report longitudinal characterization of the murine *Hdh*^{(CAG)¹⁵⁰} knock-in model of HD. A series of behavioral tests at five different time points (20, 40, 50, 70, and 100 weeks) demonstrates an age-dependent, late-onset behavioral phenotype with significant motor abnormalities at 70 and 100 weeks of age. Pathological analysis demonstrated loss of striatal dopamine D₁ and D₂ receptor binding sites at 70 and 100 weeks of age, and stereological analysis showed significant loss of striatal neuron number at 100 weeks. Late-onset behavioral abnormalities, decrease in striatal dopamine receptors, and diminished striatal neuron number observed in this mouse model recapitulate key features of HD. The *Hdh*^{(CAG)¹⁵⁰} knock-in mouse is a valid model to evaluate early events in the pathogenesis of neurodegeneration in HD.

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Sulfatide Storage in Neurons Causes Hyperexcitability and Axonal Degeneration in a Mouse Model of Metachromatic Leukodystrophy

Matthias Eckhardt,¹ Kerstin Khalaj Hedayati,⁴ Julika Pitsch,² Renate Lüllmann-Rauch,⁴ Heinz Beck,³ Simon Ngamli Fewou,¹ and Volkmar Gieselmann¹

¹Institute of Physiological Chemistry and Departments of ²Neuropathology and ³Epileptology, University of Bonn, 53115 Bonn, Germany, and ⁴Institute of Anatomy, University of Kiel, 24098 Kiel, Germany

Metachromatic leukodystrophy is a lysosomal storage disorder caused by deficiency in the sulfolipid degrading enzyme arylsulfatase A (ASA). In the absence of a functional ASA gene, 3-O-sulfogalactosylceramide (sulfatide; SGalCer) and other sulfolipids accumulate. The storage is associated with progressive demyelination and various finally lethal neurological symptoms. Lipid storage, however, is not restricted to myelin-producing cells but also occurs in neurons. It is unclear whether neuronal storage contributes to symptoms of the patients. Therefore, we have generated transgenic ASA-deficient [ASA(-/-)] mice overexpressing the sulfatide synthesizing enzymes UDP-galactose:ceramide galactosyltransferase (CGT) and cerebroside sulfotransferase (CST) in neurons to provoke neuronal lipid storage. CGT-transgenic ASA(-/-) [CGT/ASA(-/-)] mice showed an accumulation of C18:0 fatty acid-containing SGalCer in the brain. Histochemically, an increase in sulfolipid storage could be detected in central and peripheral neurons of both CGT/ASA(-/-) and CST/ASA(-/-) mice compared with ASA(-/-) mice. CGT/ASA(-/-) mice developed severe neuromotor coordination deficits and weakness of hindlimbs and forelimbs. Light and electron microscopic analyses demonstrated nerve fiber degeneration in the spinal cord of CGT/ASA(-/-) mice. CGT/ASA(-/-) and, to a lesser extent, young ASA(-/-) mice exhibited cortical hyperexcitability, with recurrent spontaneous cortical EEG discharges lasting 5–15 s. These observations suggest that SGalCer accumulation in neurons contributes to disease phenotype.

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Angiotensin II Controls Occludin Function and Is Required for Blood–Brain Barrier Maintenance: Relevance to Multiple Sclerosis

Karolina Wosik,^{1*} Romain Cayrol,^{1*} Aurore Dodelet-Devillers,¹ France Berthelet,² Monique Bernard,¹ Robert Mouldjian,³ Alain Bouthillier,³ Timothy L. Reudelhuber,⁵ and Alexandre Prat^{1,4,6}

¹Neuroimmunology Research Laboratory, Center for Study of Brain Diseases, ²Department of Neuropathology, ³Department of Neurosurgery, ⁴Department of Neurology, ⁵Laboratory of Molecular Biochemistry of Hypertension, Clinical Research Institute of Montreal, and ⁶Multiple Sclerosis Clinic, Department of Neurology, Centre Hospitalier de l'Université de Montréal–Notre Dame Hospital, University of Montreal, Montréal, Quebec, Canada H2L 4M1

The blood–brain barrier (BBB) restricts molecular and cellular trafficking between the blood and the CNS. Although astrocytes are known to control BBB permeability, the molecular determinants of this effect remain unknown. We show that angiotensinogen (AGT) produced and secreted by astrocytes is cleaved into angiotensin II (AngII) and acts on type 1 angiotensin receptors (AT₁) expressed by BBB endothelial cells (ECs). Activation of AT₁ restricts the passage of molecular tracers across human BBB-derived ECs through threonine-phosphorylation of the tight junction protein occludin and its mobilization to lipid raft membrane microdomains. We also show that AGT knock-out animals have disorganized occludin strands at the level of the BBB and a diffuse accumulation of the endogenous serum protein plasminogen in the CNS, compared with wild-type animals. Finally, we demonstrate a reduction in the number of AGT-immunopositive perivascular astrocytes in multiple sclerosis (MS) lesions, which correlates with a reduced expression of occludin similarly seen in the CNS of AGT knock-out animals. Such a reduction in astrocyte-expressed AGT and AngII is dependent, *in vitro*, on the proinflammatory cytokines tumor necrosis factor- α and interferon- γ . Our study defines a novel physiological role for AngII in the CNS and suggests that inflammation-induced downregulation of AngII production by astrocytes is involved in BBB dysfunction in MS lesions.

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Dark Rearing Rescues P23H Rhodopsin-Induced Retinal Degeneration in a Transgenic *Xenopus laevis* Model of Retinitis Pigmentosa: A Chromophore-Dependent Mechanism Characterized by Production of N-Terminally Truncated Mutant Rhodopsin

Beatrice M. Tam and Orson L. Moritz

Department of Ophthalmology and Visual Sciences, Centre for Macular Research, University of British Columbia, Vancouver, British Columbia, Canada V5Z 3N9

To elucidate the molecular mechanisms underlying the light-sensitive retinal degeneration caused by the rhodopsin mutation P23H, which causes retinitis pigmentosa (RP) in humans, we expressed *Xenopus laevis*, bovine, human, and murine forms of P23H rhodopsin in transgenic *X. laevis* rod photoreceptors. All P23H rhodopsins caused aggressive retinal degeneration associated with low expression levels and retention of P23H rhodopsin in the endoplasmic reticulum (ER), suggesting involvement of protein misfolding and ER stress. However, light sensitivity varied dramatically between these RP models, with complete or partial rescue by dark rearing in the case of bovine and human P23H rhodopsin, and no rescue for *X. laevis* P23H rhodopsin. Rescue by dark rearing required an intact 11-*cis*-retinal chromophore binding site within the mutant protein and was associated with truncation of the P23H rhodopsin N terminus. This yielded an abundant nontoxic ~27 kDa form that escaped the ER and was transported to the rod outer segment. The truncated protein was produced in the greatest quantities in dark-reared retinas expressing bovine P23H rhodopsin and was not observed with *X. laevis* P23H rhodopsin. These results are consistent with a mechanism involving enhanced protein folding in the presence of 11-*cis*-retinal chromophore, with ER exit assisted by proteolytic truncation of the N terminus. This study provides a molecular mechanism for light sensitivity observed in other transgenic models of RP and for phenotypic variation among RP patients.

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Immunotherapy Targeting Pathological Tau Conformers in a Tangle Mouse Model Reduces Brain Pathology with Associated Functional Improvements

Ayodeji A. Asuni,¹ Allal Boutajangout,¹ David Quartermain,² and Einar M. Sigurdsson^{1,3}

Departments of ¹Psychiatry, ²Neurology, and ³Pathology, New York University School of Medicine, New York, New York 10016

Immunotherapies for various neurodegenerative diseases have recently emerged as a promising approach for clearing pathological protein conformers in these disorders. This type of treatment has not been assessed in models that develop neuronal tau aggregates as observed in frontotemporal dementia and Alzheimer's disease. Here, we present that active immunization with a phosphorylated tau epitope, in P301L tangle model mice, reduces aggregated tau in the brain and slows progression of the tangle-related behavioral phenotype. Females had more tau pathology than males but were also more receptive to the immunotherapy. The tau antibodies generated in these animals recognized pathological tau on brain sections. Performance on behavioral assays that require extensive motor coordination correlated with tau pathology in corresponding brain areas, and antibody levels against the immunogen correlated inversely with tau pathology. Interestingly, age-dependent autoantibodies that recognized recombinant tau protein but not the immunogen were detected in the P301L mice. To confirm that anti-tau antibodies could enter the brain and bind to pathological tau, FITC-tagged antibodies purified from a P301L mouse, with a high antibody titer against the immunogen, were injected into the carotid artery of P301L mice. These antibodies were subsequently detected within the brain and colocalized with PHF1 and MC1 antibodies that recognize pathological tau. Currently, no treatment is available for clearing tau aggregates. Our present findings may lead to a novel therapy targeting one of the major hallmarks of Alzheimer's disease and frontotemporal dementia.

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The Tau N279K Exon 10 Splicing Mutation Recapitulates Frontotemporal Dementia and Parkinsonism Linked to Chromosome 17 Tauopathy in a Mouse Model

Hana N. Dawson, Viviana Cantillana, Liling Chen, and Michael P. Vitek

Division of Neurology, Duke University, Durham, North Carolina 27710

Intracellular tau deposits are characteristic of several neurodegenerative disorders called tauopathies. The tau protein regulates the stability and assembly of microtubules by binding to microtubules through three or four microtubule-binding repeats (3R and 4R). The number of microtubule-binding repeats is determined by the inclusion or exclusion of the second microtubule-binding repeat encoded by exon 10 of the *TAU* gene. *TAU* gene mutations that alter the inclusion of exon 10, and hence the 4R:3R ratio, are causal in the tauopathy frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). A mutation located in exon 10 has been identified in several FTDP-17 families that present with increased exon 10 inclusion in both mRNA and protein, parkinsonism, movement disorders, and dementia. We have engineered a human tau minigene construct that was designed to allow alternative splicing of the tau exon 10. Here we demonstrate that transgenic mice expressing human tau protein with this mutation develop neurodegeneration as result of aberrant splicing. The mice recapitulate many of the disease hallmarks that are seen in patients with this mutation, including increased tau exon 10 inclusion in both mRNA and protein, motor and behavioral deficits, and tau protein accumulation in neurons and tufted astrocytes. Furthermore, these mice present with degeneration of the nigrostriatal dopaminergic pathway, suggesting a possible mechanism for parkinsonism in FTDP-17. Additionally, activated caspase-3 immunoreactivity in both neurons and astrocytes implicates the involvement of the apoptotic pathway in the pathology of these mice.

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Microarray Analysis of the Cellular Pathways Involved in the Adaptation to and Progression of Motor Neuron Injury in the SOD1 G93A Mouse Model of Familial ALS

Laura Ferraiuolo, Paul R. Heath, Hazel Holden, Paul Kasher, Janine Kirby, and Pamela J. Shaw

Academic Neurology Unit, Section of Neuroscience, School of Medicine and Biomedical Sciences, University of Sheffield, Sheffield S10 2RX, United Kingdom

The cellular pathways of motor neuronal injury have been investigated in the SOD1 G93A murine model of familial amyotrophic lateral sclerosis (ALS) using laser-capture microdissection and microarray analysis. The advantages of this study include the following: analysis of changes specifically in motor neurons (MNs), while still detecting effects of interactions with neighboring cells; the ability to profile changes during disease progression, an approach not possible in human ALS; and the use of transgenic mice bred on a homogeneous genetic background, eliminating the confounding effects arising from a mixed genetic background. By using this rigorous approach, novel changes in key cellular pathways have been detected at both the presymptomatic and late stages, which have been validated by quantitative reverse transcription-PCR.

At the presymptomatic stage (60 d), MNs extracted from SOD1 G93A mice show a significant increase in expression of genes subserving both transcriptional and translational functions, as well as lipid and carbohydrate metabolism, mitochondrial preprotein translocation, and respiratory chain function, suggesting activation of a strong cellular adaptive response. Mice 90 d old still show upregulation of genes involved in carbohydrate metabolism, whereas transcription and mRNA processing genes begin to show downregulation. Late in the disease course (120 d), important findings include the following: marked transcriptional repression, with downregulation of multiple transcripts involved in transcriptional and metabolic functions; upregulation of complement system components; and increased expression of key cyclins involved in cell-cycle regulation. The changes described in the motor neuron transcriptome evolving during the disease course highlight potential novel targets for neuroprotective therapeutic intervention.

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Different Species of α -Synuclein Oligomers Induce Calcium Influx and Seeding

Karin M. Danzer,¹ Dorothea Haasen,² Anne R. Karow,¹ Simon Moussaud,¹ Matthias Habeck,³ Armin Giese,³ Hans Kretzschmar,³ Bastian Hengerer,¹ and Marcus Kostka¹

¹Central Nervous System Research and ²Integrated Drug Discovery, Boehringer Ingelheim Pharma, 88397 Biberach, Germany, and ³Zentrum für Neuropathologie und Prionforschung, Ludwig-Maximilians Universität München, 81377 München, Germany

Aggregation of α -synuclein (α -syn) has been linked to the pathogenesis of Parkinson's disease (PD) and other neurodegenerative diseases. Increasing evidence suggests that prefibrillar oligomers and protofibrils, rather than mature fibrils of α -syn, are the pathogenic species in PD. Despite extensive effort on studying oligomerization of α -syn, no studies have compared different oligomer species directly on a single-particle level and investigated their biological effects on cells. In this study, we applied a novel highly sensitive single molecule detection system that allowed a direct comparison of different oligomer types. Furthermore, we studied biological effects of different oligomer types on cells. For this purpose, we developed new oligomerization protocols, that enabled the use of these different oligomers in cell culture. We found that all of our three aggregation protocols resulted in heterogeneous populations of oligomers. Some types of oligomers induced cell death via disruption of cellular ion homeostasis by a presumably pore-forming mechanism. Other oligomer types could directly enter the cell resulting in increased α -syn aggregation. Based on our results, we propose that under various physiological conditions, heterogeneous populations of oligomeric forms will coexist in an equilibrium. These different oligomer types lead directly or indirectly to cell damage. Our data indicate that inhibition of early α -syn aggregation events would consequently prevent all α -syn oligomer related toxicities. This has important implications for the development of disease-modifying drugs for the treatment of PD and other synucleinopathies.

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