

This Week in The Journal

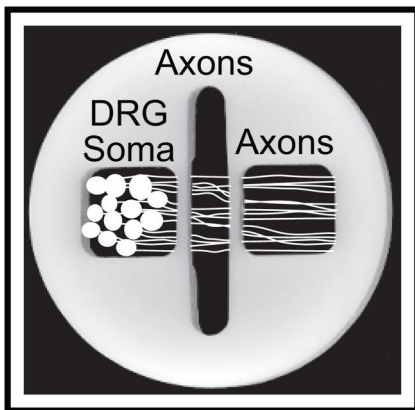
● Cellular/Molecular

DRG-Derived BDNF and Myelination

Benjamin K. Ng, Lian Chen, Wilhelm Mandemakers, José M. Cosgaya, and Jonah R. Chan

(see pages 7597–7603)

Although neurotrophic factors are usually considered to be target-derived secretory products that are then retrogradely transported to their site of action, this week Ng et al. provide more proof that BDNF can move in other directions. The authors examined the source of BDNF necessary for Schwann cell-mediated myelination of sensory nerves. BDNF expression increased soon after purified Schwann cells were cocultured with dorsal root ganglion (DRG) neurons. The expression was greatest prior to myelination. Using Campenot chambers, the authors report that BDNF was secreted from the compartment containing DRG axons as well as the cell body compartment, consistent with anterograde transport and secretion from the surface of the axons. Viral-mediated gene transfer of myc-tagged BDNF into DRGs was later detected in Schwann cells, consistent with transfer of BDNF from DRG to Schwann cell. Overexpression of BDNF in DRGs also led to anterograde transport, secretion, and enhanced myelination.



DRGs were cultured in Campenot chambers, which allowed analysis of BDNF secretion from cell bodies and axons. See the article by Ng et al. for details.

▲ Development/Plasticity/Repair

Making Shaft Synapses

Jason Aoto, Pamela Ting, Bita Maghsoodi, Nanjie Xu, Mark Henkemeyer, and Lu Chen

(see pages 7508–7519)

Although excitatory synapses on dendritic spines seem to get most of the experimental attention, a subset of excitatory synapses end up on dendritic shafts. In some cells after all, such as many interneurons, there are no dendritic spines. Synapses on shafts are predicted to have distinct impacts on cell excitability based on differences in synaptic size and the electrotonic properties of dendrites. This week, Aoto et al. show that the formation of shaft synapses in cultured hippocampal pyramidal cells depends on so-called reverse ephrinB3 signaling. Reducing postsynaptic ephrinB3 by RNA interference decreased shaft synapses, whereas overexpression of ephrinB3 increased them. The effects of ephrin B3 knockdown were reversed by overexpression of the glutamate receptor-interacting protein 1 (GRIP1). Reverse ephrin signaling contrasts with forward ephrin signaling in which presynaptic ephrinBs promote spine synapse formation as a result of activation of postsynaptic EphB receptors.

■ Behavioral/Systems/Cognitive

*Sensorimotor Integration in *C. elegans**

Christopher V. Gabel, Harrison Gabel, Dmitri Pavlichin, Albert Kao, Damon A. Clark, and Aravinthan D. T. Samuel

(see pages 7586–7596)

This week, Gabel et al. show that worms have a good understanding of high school physics even without reading the textbook. The authors placed worms within an electric field and observed, as expected, that the worms crawled toward the negative pole. The threshold field strength was about 3 V/cm. How-

ever, rather than going directly for the pole, the worms followed an angular path that corresponded to the force lines in the electrical field. Time-varying fields caused the worms to reverse and turn. For example, steady rotation of the field caused worms to crawl in perfect circles for hours, perhaps similar to rotary traffic during a Boston rush hour. Laser ablation of amphid sensory neurons, particularly ASJ or ASH, disrupted this electrosensory behavior. These neurons were sensitive to the direction and strength of electric fields as measured by calcium imaging of immobilized worms. The behavior may provide a useful model system for sensorimotor integration.

◆ Neurobiology of Disease

GABA_A Receptor Localization in Epileptic Mice

Nianhui Zhang, Weizheng Wei, Istvan Mody, and Carolyn R. Houser

(see pages 7520–7531)

The subunit composition of GABA_A receptors determines in part whether GABA-mediated inhibition is phasic or tonic. For example, δ and $\alpha 4$ subunits are often expressed in GABA_A receptors that mediate tonic inhibition at perisynaptic or extrasynaptic locations. In contrast, $\gamma 2$ subunits are generally located at synapses and are involved in phasic inhibition. This week, Zhang et al. examined the location of these GABA_A receptor subunits in mice rendered epileptic by pilocarpine treatment, a standard animal model of temporal lobe epilepsy. Postembedding immunogold labeling confirmed a perisynaptic decrease in the δ subunit in dentate granule cell dendrites within the molecular layer. However, physiological studies found that tonic inhibition was still present. The $\gamma 2$ subunits shifted toward perisynaptic locations in the epileptic mice in parallel with a decrease in phasic inhibition. The authors suggest that receptors containing $\alpha 4$ and relocated $\gamma 2$ may underlie tonic inhibition in the epileptic mice.

The Journal of Neuroscience

July 11, 2007 • Volume 27 Number 28 www.jneurosci.org



Cover legend: At one bank of the river (top), the apical dendritic trees of hippocampal pyramidal neurons show reduced expression of NR1 subunit and severe loss of synaptic NMDA receptor currents, resembling a leafless tree in a winter landscape. On the other bank (bottom), the apical dendritic trees of normal hippocampal pyramidal neurons display dendritic spines stained in red. For more information, see the article by Alvarez et al. in this issue (pages 7377–7385).

i This Week in The Journal

Journal Club

- 7363 **Spatial Updating in a Three-Dimensional World**
Suzanne Ryan, Åsa Pellijeff, Catherine Preston, and Kirsten McKenzie

Brief Communications

- 7553 **An Early Critical Period for Long-Term Plasticity and Structural Modification of Sensory Synapses in Olfactory Cortex**
Cindy Poo and Jeffrey S. Isaacson
- 7559 **Perisaccadic Compression Correlates with Saccadic Peak Velocity: Differential Association of Eye Movement Dynamics with Perceptual Mislocalization Patterns**
Florian Ostendorf, Constance Fischer, Carsten Finke, and Christoph J. Ploner

Articles

CELLULAR/MOLECULAR

- 7365 **Distinct Structural and Ionotropic Roles of NMDA Receptors in Controlling Spine and Synapse Stability**
Veronica A. Alvarez, Dennis A. Ridenour, and Bernardo L. Sabatini
- 7377 **Short-Term Depression at the Reciprocal Synapses between a Retinal Bipolar Cell Terminal and Amacrine Cells**
Geng-Lin Li, Jozsef Vigh, and Henrique von Gersdorff
- 7418 **Nuclear Localization of Ataxin-3 Is Required for the Manifestation of Symptoms in SCA3: *In Vivo* Evidence**
Ulrike Bichelmeier, Thorsten Schmidt, Jeannette Hübener, Jana Boy, Lukas Rüttiger, Karina Häbig, Sven Poths, Michael Bonin, Marlies Knipper, Werner J. Schmidt, Johannes Wilbertz, Hartwig Wolburg, Franco Laccone, and Olaf Riess
- 7438 **Endogenous Alkaline Transients Boost Postsynaptic NMDA Receptor Responses in Hippocampal CA1 Pyramidal Neurons**
Sachin Makani and Mitchell Chesler
- 7447 **Induction of Calcium Influx through TRPC5 Channels by Cross-Linking of GM1 Ganglioside Associated with $\alpha 5\beta 1$ Integrin Initiates Neurite Outgrowth**
Gusheng Wu, Zi-Hua Lu, Alexander G. Obukhov, Martha C. Nowycky, and Robert W. Ledeen
- 7469 **High Cyclophilin D Content of Synaptic Mitochondria Results in Increased Vulnerability to Permeability Transition**
Kranthi Kumari Naga, Patrick G. Sullivan, and James W. Geddes

7578 **Contribution of the Putative Inner-Pore Region to the Gating of the Transient Receptor Potential Vanilloid Subtype 1 Channel (TRPV1)**
Klara Susankova, Rudiger Ettrich, Ladislav Vyklicky, Jan Teisinger, and Viktorie Vlachova

7597 **Anterograde Transport and Secretion of Brain-Derived Neurotrophic Factor along Sensory Axons Promote Schwann Cell Myelination**
Benjamin K. Ng, Lian Chen, Wilhelm Mandemakers, José M. Cosgaya, and Jonah R. Chan

DEVELOPMENT/PLASTICITY/REPAIR

7397 **BMPRIa Signaling Determines Numbers of Oligodendrocytes and Calbindin-Expressing Interneurons in the Cortex**
Jayshree Samanta, Gordon M. Burke, Tammy McGuire, Anna J. Pisarek, Abhishek Mukhopadhyay, Yuji Mishina, and John A. Kessler

7408 **Mode of Action and Functional Significance of Estrogen-Inducing Dendritic Growth, Spinogenesis, and Synaptogenesis in the Developing Purkinje Cell**
Katsunori Sasahara, Hanako Shikimi, Shogo Haraguchi, Hirotaaka Sakamoto, Shin-ichiro Honda, Nobuhiro Harada, and Kazuyoshi Tsutsui

7508 **Postsynaptic EphrinB3 Promotes Shaft Glutamatergic Synapse Formation**
Jason Aoto, Pamela Ting, Bitu Maghsoodi, Nanjie Xu, Mark Henkemeyer, and Lu Chen

7541 **Pilocarpine-Induced Seizures Cause Selective Time-Dependent Changes to Adult-Generated Hippocampal Dentate Granule Cells**
Cynthia Walter, Brian L. Murphy, Raymund Y. K. Pun, Anne L. Spieles-Engemann, and Steve C. Danzer

BEHAVIORAL/SYSTEMS/COGNITIVE

7386 **Role of the Primate Amygdala in Fear-Potentiated Startle: Effects of Chronic Lesions in the Rhesus Monkey**
Elena A. Antoniadis, James T. Winslow, Michael Davis, and David G. Amaral

7459 **Nonthermal Activation of Transient Receptor Potential Vanilloid-1 Channels in Abdominal Viscera Tonicly Inhibits Autonomic Cold-Defense Effectors**
Alexandre A. Steiner, Victoria F. Turek, Maria C. Almeida, Jeffrey J. Burmeister, Daniela L. Oliveira, Jennifer L. Roberts, Anthony W. Bannon, Mark H. Norman, Jean-Claude Louis, James J. S. Treanor, Narendra R. Gavva, and Andrej A. Romanovsky

7476 **Induction of Long-Term Memory by Exposure to Novelty Requires Protein Synthesis: Evidence for a Behavioral Tagging**
Diego Moncada and Haydée Viola

7482 **Impact of Commitment on Performance Evaluation in the Rostral Cingulate Motor Area**
Thomas Michelet, Bernard Bioulac, Dominique Guehl, Ludovic Escola, and Pierre Burbaud

7490 **Psychophysical and Physiological Evidence for Parallel Afferent Pathways Mediating the Sensation of Itch**
Lisa M. Johaneck, Richard A. Meyer, Tim Hartke, Joseph Greg Hobelmann, David N. Maine, Robert H. LaMotte, and Matthias Ringkamp

7498 **Direct Instrumental Conditioning of Neural Activity Using Functional Magnetic Resonance Imaging-Derived Reward Feedback**
Signe Bray, Shinsuke Shimojo, and John P. O'Doherty

- 7532 **Chronic Mild Stress during Gestation Worsens Neonatal Brain Lesions in Mice**
 Claire-Marie Rangon, Silvia Fortes, Vincent Lelièvre, Philippe Leroux,
 Frank Plaisant, Chantal Joubert, Laurence Lanfumey, Charles Cohen-Salmon, and
 Pierre Gressens
- 7564 **Lesions of the Tegmentomammillary Circuit in the Head Direction System Disrupt the
 Head Direction Signal in the Anterior Thalamus**
 Joshua P. Bassett, Matthew L. Tullman, and Jeffrey S. Taube
- 7586 **Neural Circuits Mediate Electrosensory Behavior in *Caenorhabditis elegans***
 Christopher V. Gabel, Harrison Gabel, Dmitri Pavlichin, Albert Kao,
 Damon A. Clark, and Aravinthan D. T. Samuel
- 7604 **A Novel Molecule “Shati” Is Involved in Methamphetamine-Induced
 Hyperlocomotion, Sensitization, and Conditioned Place Preference**
 Minae Niwa, Atsumi Nitta, Hiroyuki Mizoguchi, Yasutomo Ito, Yukihiko Noda,
 Taku Nagai, and Toshitaka Nabeshima

NEUROBIOLOGY OF DISEASE

- 7429 **Lymphotoxin β Receptor (Lt β R): Dual Roles in Demyelination and Remyelination
 and Successful Therapeutic Intervention Using Lt β R-Ig Protein**
 Sheila R. Plant, Heather A. Iocca, Ying Wang, J. Cameron Thrash,
 Brian P. O’Connor, Heather A. Arnett, Yang-Xin Fu, Monica J. Carson, and
 Jenny P.-Y. Ting
- 7520 **Altered Localization of GABA_A Receptor Subunits on Dentate Granule Cell Dendrites
 Influences Tonic and Phasic Inhibition in a Mouse Model of Epilepsy**
 Nianhui Zhang, Weizheng Wei, Istvan Mody, and Carolyn R. Houser

Correction: In the article “Impairments in Fast Axonal Transport and Motor Neuron Deficits in Transgenic Mice Expressing Familial Alzheimer’s Disease-Linked Mutant Presenilin 1” by Orly Lazarov, Gerardo A. Morfini, Gustavo Pigino, Archana Gadadhar, Xiangjun Chen, John Robinson, Hanson Ho, Scott T. Brady, and Sangram S. Sisodia, which appeared on pages 7011–7020 of the June 27, 2007 issue, there was an error in the Acknowledgments footnote. The correct footnote is as follows: “This work was supported by National Institutes of Health Grant AG021494 (S.S.S.), National Institute of Neurological Disorders and Stroke Grants NS23868, NS23320, NS41170, and NS43408 (S.T.B.), and the Huntington’s Disease Society of America (G.A.M.). We thank Evelyn Nwabuisi and Bin Wang for their excellent technical assistance. S.S.S. is a paid consultant of Neuropharma Inc., Eisai Labs Inc., and Torrey Pines Therapeutics Inc.”

Persons interested in becoming members of the Society for Neuroscience should contact the Membership Department, Society for Neuroscience, 1121 14th St., NW, Suite 1010, Washington, DC 20005, phone 202-962-4000.

Instructions for Authors are available at <http://www.jneurosci.org/misc/itoa.shtml>. Authors should refer to these Instructions online for recent changes that are made periodically.

Brief Communications Instructions for Authors are available via Internet (http://www.jneurosci.org/misc/ifa_bc.shtml).

Submissions should be submitted online using the following url:
<http://sfn.manuscriptcentral.com>. Please contact the Central Office, via phone, fax, or e-mail with any questions. Our contact information is as follows: phone, 202-962-4000; fax, 202-962-4945; e-mail, jn@sfn.org.

BRIEF COMMUNICATIONS

An Early Critical Period for Long-Term Plasticity and Structural Modification of Sensory Synapses in Olfactory Cortex

Cindy Poo and Jeffrey S. Isaacson

Department of Neuroscience, University of California, San Diego, School of Medicine, La Jolla, California 92093

Critical periods for plasticity of thalamic sensory inputs play an important role in developing neocortical circuits. During an early postnatal time window, pyramidal cells of visual, auditory, and somatosensory cortex undergo structural refinement and possess an enhanced ability for activity-dependent synaptic plasticity. In olfactory cortex, however, pyramidal cells receive direct sensory input from the olfactory bulb, and it is unclear whether the development of olfactory sensory circuits is governed by a critical period. Here, we show that NMDA receptor-dependent long-term potentiation and dendritic spine maturation occur only during a brief postnatal time window at sensory synapses of olfactory cortex pyramidal cells. In contrast, associational synapses onto the same cells retain the capacity for plasticity into adulthood.

The Journal of Neuroscience, July 11, 2007 • 27(28):7553–7558

Perisaccadic Compression Correlates with Saccadic Peak Velocity: Differential Association of Eye Movement Dynamics with Perceptual Mislocalization Patterns

Florian Ostendorf, Constance Fischer, Carsten Finke, and Christoph J. Ploner

Klinik für Neurologie, Charité, 10117 Berlin, Germany

Objects flashed around the onset of a saccadic eye movement are grossly mislocalized. Perisaccadic mislocalization has been related to a spatiotemporal misalignment of an extraretinal eye position signal with the corresponding saccade. Two phenomena have been observed: a systematic shift of perceived positions in saccade direction and an additional compression toward the saccade target. At present, it is unclear whether these two components of mislocalization are mediated by distinct mechanisms and how extraretinal signals may contribute to either of them. Moreover, the pattern and strength of perisaccadic mislocalization varies considerably across studies and even between subjects tested under identical conditions. Here, we investigated whether interindividual differences in saccade parameters are related to differences in mislocalization. We found that the individual strength of perceptual compression selectively correlates with the peak velocity of corresponding saccades. Other saccade parameters did not correlate with compression. No correlation was found between the shift component of perisaccadic mislocalization and any saccade parameter. This dissociation suggests that shift and compression components are, at least partially, mediated by distinct mechanisms. Because neuronal activity in the superior colliculus and downstream oculomotor areas has been shown to correlate with saccadic peak velocity, our findings support the notion that a reafferent extraretinal signal associated with saccadic motor commands may contribute to perisaccadic compression of perceived positions.

The Journal of Neuroscience, July 11, 2007 • 27(28):7559–7563

Articles

CELLULAR/MOLECULAR

Distinct Structural and Ionotropic Roles of NMDA Receptors in Controlling Spine and Synapse Stability

Veronica A. Alvarez, Dennis A. Ridenour, and Bernardo L. Sabatini

Department of Neurobiology, Harvard Medical School, Boston, Massachusetts 02115

NMDA-type glutamate receptors (NMDARs) play a central role in the rapid regulation of synaptic transmission, but their contribution to the long-term stabilization of glutamatergic synapses is unknown. We find that, in hippocampal pyramidal neurons in rat organotypic slices, pharmacological blockade of NMDARs does not affect synapse formation and dendritic spine growth but does increase the motility of spines. Physical loss of synaptic NMDARs induced by RNA interference against the NR1 subunit of the receptor also increases the motility of spines. Furthermore, knock-down of NMDARs, but not their pharmacological block, destabilizes spine structure and over time leads to loss of spines and excitatory synapses. Maintenance of normal spine density requires the coexpression of two specific splice isoforms of the NR1 subunit that contain the C-terminal C2 cassette. Thus, although ionotropic properties of NMDARs induce synaptic plasticity, it is the physical interactions of the C-tail of the receptor that mediate the long-term stabilization of synapses and spines.

The Journal of Neuroscience, July 11, 2007 • 27(28):7365–7376

Short-Term Depression at the Reciprocal Synapses between a Retinal Bipolar Cell Terminal and Amacrine Cells

Geng-Lin Li, Jozsef Vigh, and Henrique von Gersdorff

The Vollum Institute, Oregon Health and Science University, Portland, Oregon 97239

Visual adaptation is thought to occur partly at retinal synapses that are subject to plastic changes. However, the locus and properties of this plasticity are not well known. Here, we studied short-term plasticity at the reciprocal synapse between bipolar cell terminals and amacrine cells in goldfish retinal slices. Depolarization of a single bipolar cell terminal for 100 ms triggers the release of glutamate onto amacrine cell processes, which in turn leads to GABAergic feedback from amacrine cells onto the same terminal. We find that this release of GABA undergoes paired-pulse depression (PPD) that recovers in <1 min (single exponential time constant, $\tau \cong 12$ s). This disynaptic PPD is independent of mGluR-mediated plasticity and depletion of glutamatergic synaptic vesicle pools, because exocytosis assayed via capacitance jumps (ΔC_m) recovered completely after 10 s ($\tau \cong 2$ s). Fast application of GABA (10 mM) onto outside-out patches excised from bipolar cell terminals showed that the recovery of GABA_A receptors from desensitization depends on the duration of the application [fast recovery (<2 s) for short applications; slow ($\tau \cong 12$ s) for prolonged applications]. We thus blocked GABA_A receptors and retested the GABAergic response mediated by nondesensitizing GABA_C receptors to two rapid glutamate puffs onto the bipolar cell terminal. These responses consistently displayed PPD. Furthermore, blocking AMPA-receptor desensitization with cyclothiazide, or evoking GABA release with NMDA receptors, did not reduce PPD. We thus suggest that depletion of synaptic vesicle pools in GABAergic amacrine cells is a major contributor to PPD.

The Journal of Neuroscience, July 11, 2007 • 27(28):7377–7385

Nuclear Localization of Ataxin-3 Is Required for the Manifestation of Symptoms in SCA3: *In Vivo* Evidence

Ulrike Bichelmeier,¹ Thorsten Schmidt,¹ Jeannette Hübener,¹ Jana Boy,¹ Lukas Rüttiger,² Karina Häbig,¹ Sven Poths,¹ Michael Bonin,¹ Marlies Knipper,² Werner J. Schmidt,^{3†} Johannes Wilbertz,⁵ Hartwig Wolburg,⁴ Franco Laccone,⁶ and Olaf Riess¹

Departments of ¹Medical Genetics and ²Otorhinolaryngology, ³Zoological Institute, Neuropharmacology, and ⁴Institute for Pathology, University of Tübingen, D-72076 Tübingen, Germany, ⁵Department of Cell and Molecular Biology, Karolinska Institute, SE-171 77 Stockholm, Sweden, and ⁶Department of Medical Genetics, University of Vienna, A-1090 Vienna, Austria

Spinocerebellar ataxia type 3 (SCA3) is an autosomal dominantly inherited neurodegenerative disorder caused by the expansion of a CAG repeat in the *MJD1* gene resulting in an expanded polyglutamine repeat in the ataxin-3 protein. To study the course of the disease, we generated transgenic mice for SCA3 using full-length ataxin-3 constructs containing 15, 70, or 148 CAG repeats, respectively. Control mice (15 CAGs) were phenotypically normal and had no neuropathological findings. However, mice transgenic for ataxin-3 with expanded polyglutamine repeats were severely affected by a strong neurological phenotype with tremor, behavioral deficits, strongly reduced motor and exploratory activity, a hunchback, and premature death at 3 to 6 months of age. Neuropathological examination by immunohistochemical staining revealed ubiquitin- and ataxin-3-positive intranuclear inclusion bodies in a multitude of neurons. Directing ataxin-3 with 148 CAGs to the nucleus revealed an even more pronounced phenotype with more inclusions and earlier death, whereas mice transgenic with the same construct but attached to a nuclear export signal developed a milder phenotype with less inclusions. These studies indicate that nuclear localization of ataxin-3 is required for the manifestation of symptoms in SCA3 *in vivo*.

The Journal of Neuroscience, July 11, 2007 • 27(28):7418–7428

Endogenous Alkaline Transients Boost Postsynaptic NMDA Receptor Responses in Hippocampal CA1 Pyramidal Neurons

Sachin Makani and Mitchell Chesler

Departments of Neurosurgery and Physiology and Neuroscience, New York University School of Medicine, New York, New York 10016

In hippocampus, activation of the Schaffer collaterals generates an extracellular alkaline transient both *in vitro* and *in vivo*. This pH change may provide relief of the H⁺ block of NMDA receptors (NMDARs) and thereby increase excitability. To test this hypothesis, we augmented extracellular buffering in mouse hippocampal slices by adding 2 μ M bovine type II carbonic anhydrase to the superfusate. With addition of enzyme, the alkaline transient elicited by a 10 pulse, 100 Hz stimulus train was reduced by 33%. At a holding potential (V_H) of -30 mV, the enzyme decreased the half-time of decay and charge transfer of EPSCs by 32 and 39%, respectively, but had no effect at a V_H of -80 mV. In current clamp, a 10 pulse, 100 Hz stimulus train gave rise to an NMDAR-dependent afterdepolarization (ADP). Exogenous enzyme curtailed the ADP half-width and voltage integral by 20 and 25%, respectively. Similar reduction of the ADP was noted with a brief 12 Hz stimulus train. The effect persisted in the presence of GABAergic antagonists or the L-type Ca²⁺ channel blocker methoxyverapamil hydrochloride but was absent in the presence of the carbonic anhydrase inhibitor benzolamide or when the exogenous enzyme was heat inactivated. The effects of the enzyme in voltage and current clamp were noted in 0 Mg²⁺ media but were abolished when (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5,10-imine maleate was included in the patch pipette. These results provide strong evidence that endogenous alkaline transients are sufficiently large in the vicinity of the synapse to augment NMDAR responses.

The Journal of Neuroscience, July 11, 2007 • 27(28):7438–7446

Induction of Calcium Influx through TRPC5 Channels by Cross-Linking of GM1 Ganglioside Associated with $\alpha 5\beta 1$ Integrin Initiates Neurite Outgrowth

Gusheng Wu,¹ Zi-Hua Lu,¹ Alexander G. Obukhov,² Martha C. Nowycky,² and Robert W. Ledeen^{1,2}

Departments of ¹Neurology and Neurosciences and ²Physiology and Pharmacology, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, New Jersey 07103

Previous studies demonstrated that cross-linking of GM1 ganglioside with multivalent ligands, such as B subunit of cholera toxin (CtxB), induced Ca^{2+} influx through an unidentified, voltage-independent channel in several cell types. Application of CtxB to undifferentiated NG108-15 cells resulted in outgrowth of axon-like neurites in a Ca^{2+} influx-dependent manner. In this study, we demonstrate that CtxB-induced Ca^{2+} influx is mediated by TRPC5 channels, naturally expressed in these cells and primary neurons. Both Ca^{2+} influx and neurite induction were blocked by TRPC5 small interfering RNA (siRNA). Pretreatment of NG108-15 cells with neuraminidase increased cell-surface GM1 and greatly enhanced the signal. GM1 was not directly associated with TRPC5 but rather with $\alpha 5\beta 1$ integrin, which opened the channel through a signaling sequence after cross-linking of the GM1/integrin complex. This cascade included autophosphorylation of focal adhesion kinase and subsequent activation of phospholipase $\text{C}\gamma$ (PLC γ) and phosphoinositide-3 kinase [PI(3)K]. Pharmacological blockers that inhibited tyrosine kinase, PLC, and PI(3)K suppressed both CtxB-induced Ca^{2+} influx and neurite outgrowth. These were also suppressed by SK&F96365, a nonspecific transient receptor potential channel blocker. Confocal immunocytochemistry revealed that GM1 cross-linking induced colocalization of GM1 with these signaling elements in sprouting regions of plasma membrane. In primary cerebellar granular neurons (CGNs), TRPC5 was detected at 2 d *in vitro* (2 DIV), a stage corresponding to CtxB-stimulated Ca^{2+} influx. Neurite outgrowth in CGNs, determined at 3 DIV, was accelerated by CtxB and suppressed by TRPC5 siRNA and the above blockers. The crucial role of GM1 was indicated with CGNs from ganglio-series null mice, in which growth of axons was significantly retarded.

The Journal of Neuroscience, July 11, 2007 • 27(28):7447–7458

High Cyclophilin D Content of Synaptic Mitochondria Results in Increased Vulnerability to Permeability Transition

Kranthi Kumari Naga,¹ Patrick G. Sullivan,^{1,2} and James W. Geddes^{1,2}

¹Spinal Cord and Brain Injury Research Center and ²Department of Anatomy and Neurobiology, University of Kentucky, Lexington, Kentucky 40536

Mitochondria isolated from synaptosomes are more sensitive to Ca^{2+} overload and the resultant opening of the mitochondrial permeability transition pore (mPTP) than nonsynaptic mitochondria. To identify the mechanisms underlying these differences in Ca^{2+} dynamics, we examined relative levels of mPTP components in synaptic versus nonsynaptic mitochondria. Synaptic mitochondria had higher levels of cyclophilin D when compared with nonsynaptic mitochondria, whereas levels of the voltage-dependent anion channel and the adenine nucleotide translocase were similar in the two mitochondrial fractions. These differences in Ca^{2+} handling between synaptic and nonsynaptic mitochondria were greatly reduced in cyclophilin D null [*Ppif*^{-/-} (peptidylprolyl isomerase F)] mice. Higher concentrations of cyclosporine A, which interacts with cyclophilin D to delay mPTP opening, were necessary to increase the Ca^{2+} uptake capacity of synaptic versus nonsynaptic mitochondria. To determine whether the differences in Ca^{2+} handling might reflect the relative abundance of neuronal and glial mitochondria in the two mitochondrial fractions, we compared cyclophilin D levels in primary cortical neurons and astrocytes. Primary rat cortical neurons possess higher cyclophilin D levels than do primary astrocytes. In the adult rat brain, cyclophilin D immunoreactivity was abundant in neurons but sparse in astrocytes. Together, these results demonstrate that the Ca^{2+} handling differences observed in synaptic versus nonsynaptic mitochondria are primarily the result of the high levels of cyclophilin D in synaptic mitochondria, reflecting the greater proportion of neuronal mitochondria in this fraction. The high levels of cyclophilin D in neuronal mitochondria result in their greater vulnerability to mPT and in higher levels of cyclosporine A being required to inhibit mPTP opening.

The Journal of Neuroscience, July 11, 2007 • 27(28):7469–7475

Contribution of the Putative Inner-Pore Region to the Gating of the Transient Receptor Potential Vanilloid Subtype 1 Channel (TRPV1)

Klara Susankova,¹ Rudiger Ettrich,² Ladislav Vyklicky,¹ Jan Teisinger,¹ and Viktorie Vlachova¹

¹Department of Cellular Neurophysiology, Institute of Physiology, Academy of Sciences of the Czech Republic, 142 20 Prague 4, Czech Republic, and

²Laboratory of High Performance Computing, Institute of Systems Biology and Ecology, Academy of Sciences of the Czech Republic and Institute of Physical Biology, University of South Bohemia, 373 33 Nove Hrad, Czech Republic

The transient receptor potential vanilloid receptor-1 (TRPV1) is a sensory neuron-specific nonselective cation channel that is gated in response to various noxious stimuli: pungent vanilloids, low pH, noxious heat, and depolarizing voltages. By its analogy to K^+ channels, the S6 inner helix domain of TRPV1 (Y666-G683) is a prime candidate to form the most constricted region of the permeation pathway and might therefore encompass an as-yet-unmapped gate of the channel. Using alanine-scanning mutagenesis, we identified 16 of 17 residues, that when mutated affected the functionality of the TRPV1 channel with respect to at least one stimulus modality. T670A was the only substitution producing the wild-type channel phenotype, whereas Y666A and N676A were nonfunctional but present at the plasma membrane. The periodicity of the functional effects of mutations within the TRPV1 inner pore region is consistent with an α -helical structure in which T670 and A680 might play the roles of two bending “hinges.”

The Journal of Neuroscience, July 11, 2007 • 27(28):7578–7585

Anterograde Transport and Secretion of Brain-Derived Neurotrophic Factor along Sensory Axons Promote Schwann Cell Myelination

Benjamin K. Ng,^{1*} Lian Chen,^{2*} Wilhelm Mandemakers,³ José M. Cosgaya,⁴ and Jonah R. Chan¹

¹Zilkha Neurogenetic Institute, Keck School of Medicine, University of Southern California, Los Angeles, California 90033, ²National Institute of Child Health and Development, National Institutes of Health, Bethesda, Maryland 20892, ³Department of Human Genetics, Katholieke Universiteit Leuven, 3000 Leuven, Belgium, and ⁴Instituto de Investigaciones Biomedicas, Consejo Superior de Investigaciones, Cientificas and Universidad Autonoma de Madrid, 28029 Madrid, Spain

The neurotrophin brain-derived neurotrophic factor (BDNF) inhibits Schwann cell (SC) migration and promotes myelination via the p75 neurotrophin receptor (NTR). Despite these recent findings, the expression, localization, and mechanism of BDNF action has yet to be determined. Here we demonstrate that the sensory neurons of the dorsal root ganglion (DRG) are a major source of BDNF during postnatal development. The expression of BDNF is initially elevated before myelination and decreases dramatically after the onset of myelination. BDNF expression is controlled in part by transcriptional regulation and the increased expression of the truncated TrkB receptor on SCs. To investigate the possible mechanism of BDNF transport and release, multicompartiment Campenot chambers were used. DRG neurons transported and secreted endogenous BDNF along the surface of axons in anterograde fashion. In an attempt to enhance myelination by SCs, DRG neurons were transduced with an adenovirus to overexpress BDNF. BDNF was transported and secreted along the axons and enhanced myelination when compared with control cocultures. Together, the events surrounding the expression, localization, and mechanism of BDNF action in DRG neurons may hint at potential therapeutic implications to efficiently promote remyelination.

The Journal of Neuroscience, July 11, 2007 · 27(28):7597–7603

DEVELOPMENT/PLASTICITY/REPAIR

BMPR1a Signaling Determines Numbers of Oligodendrocytes and Calbindin-Expressing Interneurons in the Cortex

Jayshree Samanta,¹ Gordon M. Burke,¹ Tammy McGuire,¹ Anna J. Pisarek,¹ Abhishek Mukhopadhyay,¹ Yuji Mishina,² and John A. Kessler¹

¹Department of Neurology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois 60611, and ²Laboratory of Reproductive and Developmental Toxicology, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina 27709

Progenitor cells that express the transcription factor *olig1* generate several neural cell types including oligodendrocytes and GABAergic interneurons in the dorsal cortex. The fate of these progenitor cells is regulated by a number of signals including bone morphogenetic proteins (BMPs) secreted in the dorsal forebrain. BMPs signal by binding to heteromeric serine–threonine kinase receptors formed by type I (BMPR1a, BMPR1b, Alk2) and type II (BMPRII) subunits. To determine the specific role of the BMPR1a subunit in lineage commitment by *olig1*-expressing cells, we used a *cre/loxP* genetic approach to ablate BMPR1a in these cells while leaving signaling from other subunits intact. There was a reduction in numbers of immature oligodendrocytes in the BMPR1a-null mutant brains at birth. However, by postnatal day 20, the BMPR1a-null mice had a significant increase in the number of mature and immature oligodendrocytes compared with wild-type littermates. There was also an increase in the proportion of calbindin-positive interneurons in the dorsomedial cortex of BMPR1a-null mice at birth without any change in the number of parvalbumin- or calretinin-positive cells. These effects were attributable, at least in part, to a decrease in the length of the cell cycle in subventricular zone progenitor cells. Thus, our findings indicate that BMPR1a mediates the suppressive effects of BMP signaling on oligodendrocyte lineage commitment and on the specification of calbindin-positive interneurons in the dorsomedial cortex.

The Journal of Neuroscience, July 11, 2007 · 27(28):7397–7407

Mode of Action and Functional Significance of Estrogen-Inducing Dendritic Growth, Spinogenesis, and Synaptogenesis in the Developing Purkinje Cell

Katsunori Sasahara,¹ Hanako Shikimi,¹ Shogo Haraguchi,^{1,3} Hirotaka Sakamoto,¹ Shin-ichiro Honda,² Nobuhiro Harada,² and Kazuyoshi Tsutsui^{1,3}

¹Laboratory of Brain Science, Faculty of Integrated Arts and Sciences, Hiroshima University, Higashi-Hiroshima 739-8521, Japan, ²Department of Biochemistry, School of Medicine, Fujita Health University, Aichi 470-1192, Japan, and ³Laboratory of Integrative Brain Sciences, Department of Biology, Faculty of Education and Integrated Arts and Sciences, Waseda University, Shinjuku-ku, Tokyo 169-8050, Japan

Neurosteroids are synthesized *de novo* from cholesterol in the brain. To understand neurosteroid action in the brain, data on the regio- and temporal-specific synthesis of neurosteroids are needed. Recently, we identified the Purkinje cell as an active neurosteroidogenic cell. In rodents, this neuron actively produces several neurosteroids including estradiol during neonatal life, when cerebellar neuronal circuit formation occurs. Estradiol may be involved in cerebellar neuronal circuit formation through promoting neuronal growth and neuronal synaptic contact, because the Purkinje cell expresses estrogen receptor- β (ER β). To test this hypothesis, in this study we examined the effects of estradiol on dendritic growth, spinogenesis, and synaptogenesis in the Purkinje cell using neonatal wild-type (WT) mice or cytochrome P450 aromatase knock-out (ArKO) mice. Administration of estradiol to neonatal WT or ArKO mice increased dendritic growth, spinogenesis, and synaptogenesis in the Purkinje cell. In contrast, WT mice treated with tamoxifen, an ER antagonist, or ArKO mice exhibited decreased Purkinje dendritic growth, spinogenesis, and synaptogenesis at the same neonatal period. To elucidate the mode of action of estradiol, we further examined the expression of brain-derived neurotrophic factor (BDNF) in response to estrogen actions in the neonate. Estrogen administration to neonatal WT or ArKO mice increased the BDNF level in the cerebellum, whereas tamoxifen decreased the BDNF level in

WT mice similar to ArKO mice. BDNF administration to tamoxifen-treated WT mice increased Purkinje dendritic growth. These results indicate that estradiol induces dendritic growth, spinogenesis, and synaptogenesis in the developing Purkinje cell via BDNF action during neonatal life.

The Journal of Neuroscience, July 11, 2007 • 27(28):7408–7417

Postsynaptic EphrinB3 Promotes Shaft Glutamatergic Synapse Formation

Jason Aoto,¹ Pamela Ting,¹ Bita Maghsoodi,¹ Nanjie Xu,³ Mark Henkemeyer,³ and Lu Chen^{1,2}

¹Department of Molecular and Cell Biology and ²Helen Wills Neuroscience Institute, University of California, Berkeley, California 94720-3200, and

³Department of Developmental Biology and Kent Waldrep Center for Basic Research on Nerve Growth and Regeneration, University of Texas Southwestern Medical Center, Dallas, Texas 75390

Excitatory synapses in the CNS are formed on both dendritic spines and shafts. Recent studies show that the density of shaft synapses may be independently regulated by behavioral learning and the induction of synaptic plasticity, suggesting that distinct mechanisms are involved in regulating these two types of synapses. Although the molecular mechanisms underlying spinogenesis and spine synapse formation are being delineated, those regulating shaft synapses are still unknown. Here, we show that postsynaptic ephrinB3 expression promotes the formation of glutamatergic synapses specifically on the shafts, not on spines. Reducing or increasing postsynaptic ephrinB3 expression selectively decreases or increases shaft synapse density, respectively. In the ephrinB3 knock-out mouse, although spine synapses are normal, shaft synapse formation is reduced in the hippocampus. Overexpression of glutamate receptor-interacting protein 1 (GRIP1) rescues ephrinB3 knockdown phenotype by restoring shaft synapse density. GRIP1 knockdown prevents the increase in shaft synapse density induced by ephrinB3 overexpression. Together, our results reveal a novel mechanism for independent modulation of shaft synapses through ephrinB3 reverse signaling.

The Journal of Neuroscience, July 11, 2007 • 27(28):7508–7519

Pilocarpine-Induced Seizures Cause Selective Time-Dependent Changes to Adult-Generated Hippocampal Dentate Granule Cells

Cynthia Walter,¹ Brian L. Murphy,^{1,3} Raymund Y. K. Pun,¹ Anne L. Spieles-Engemann,³ and Steve C. Danzer^{1,2,3}

¹Department of Anesthesia, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio 45229, ²Departments of Anesthesia and Pediatrics, University of Cincinnati, Cincinnati, Ohio 45221, and ³Program in Neuroscience, University of Cincinnati, Cincinnati, Ohio 45229

Aberrantly interconnected granule cells are characteristic of temporal lobe epilepsy. By reducing network stability, these abnormal neurons may contribute directly to disease development. Only subsets of granule cells, however, exhibit abnormalities. Why this is the case is not known. Ongoing neurogenesis in the adult hippocampus may provide an explanation. Newly generated granule cells may be uniquely vulnerable to environmental disruptions relative to their mature neighbors. Here, we determine whether there is a critical period after neuronal birth during which neuronal integration can be disrupted by an epileptogenic insult. By bromodeoxyuridine birthdating cells in green fluorescent protein-expressing transgenic mice, we were able to noninvasively label granule cells born 8 weeks before (mature), 1 week before (immature), or 3 weeks after (newborn) pilocarpine-epileptogenesis. Neuronal morphology was examined 4 and 8 weeks after pilocarpine treatment. Strikingly, almost 50% of immature granule cells exposed to pilocarpine-epileptogenesis exhibited aberrant hilar basal dendrites. In contrast, only 9% of mature granule cells exposed to the identical insult possessed basal dendrites. Moreover, newborn cells were even more severely impacted than immature cells, with 40% exhibiting basal dendrites and an additional 20% exhibiting migration defects. In comparison, <5% of neurons from normal animals exhibited either abnormality, regardless of age. Together, these data demonstrate the existence of a critical period after the birth of adult-generated neurons during which they are vulnerable to being recruited into epileptogenic neuronal circuits. Pathological brain states therefore may pose a significant hurdle for the appropriate integration of newly born endogenous, and exogenous, neurons.

The Journal of Neuroscience, July 11, 2007 • 27(28):7541–7552

BEHAVIORAL/SYSTEMS/COGNITIVE

Role of the Primate Amygdala in Fear-Potentiated Startle: Effects of Chronic Lesions in the Rhesus Monkey

Elena A. Antoniadis,^{1,2} James T. Winslow,⁴ Michael Davis,^{5,6} and David G. Amaral^{1,2,3}

¹Department of Psychiatry and Behavioral Sciences, ²California National Primate Research Center, and ³Medical Investigation of Neurodevelopmental Disorders Institute, University of California, Davis, Davis, California 95616, ⁴National Institute of Mental Health, Bethesda, Maryland 20842, and ⁵Yerkes National Primate Research Center and ⁶Department of Psychiatry and Behavioral Science and Center for Behavioral Neuroscience, Emory University, Atlanta, Georgia 30320

In experiment 1, we assessed the role of the primate amygdala and hippocampus in the acquisition of learned fear measured with fear-potentiated startle. Three groups of six rhesus monkeys were prepared with bilateral ibotenic acid lesions of the amygdaloid complex and the hippocampus or were sham operated. Selective ibotenic acid lesions of the amygdala, but not the hippocampus, blocked the acquisition of fear-potentiated startle. In experiment 2, we assessed the role of the primate amygdala in the expression of fear-potentiated startle. Surprisingly, animals that sustained amygdala damage after they successfully learned fear-potentiated startle expressed normal fear-potentiated startle, despite a complete amygdala lesion based on magnetic resonance imaging assessments. These results suggest that although the amygdala is necessary for the initial acquisition of fear-potentiated startle,

it is not necessary for the retention and expression of fear-potentiated startle. These findings are discussed in relation to the role of the amygdala in emotional learning and in cross-species comparisons of emotional behavior.

The Journal of Neuroscience, July 11, 2007 • 27(28):7386–7396

Nonthermal Activation of Transient Receptor Potential Vanilloid-1 Channels in Abdominal Viscera Tonicly Inhibits Autonomic Cold-Defense Effectors

Alexandre A. Steiner,¹ Victoria F. Turek,¹ Maria C. Almeida,¹ Jeffrey J. Burmeister,¹ Daniela L. Oliveira,¹ Jennifer L. Roberts,¹ Anthony W. Bannon,² Mark H. Norman,³ Jean-Claude Louis,² James J. S. Treanor,² Narender R. Gavva,² and Andrej A. Romanovsky¹

¹Systemic Inflammation Laboratory, Trauma Research, St. Joseph's Hospital, Phoenix, Arizona 85013, and Departments of ²Neuroscience and ³Chemistry Research and Discovery, Amgen, Thousand Oaks, California 91320

An involvement of the transient receptor potential vanilloid (TRPV) 1 channel in the regulation of body temperature (T_b) has not been established decisively. To provide decisive evidence for such an involvement and determine its mechanisms were the aims of the present study. We synthesized a new TRPV1 antagonist, AMG0347 [(*E*)-*N*-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)-3-(2-(piperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)acrylamide], and characterized it *in vitro*. We then found that this drug is the most potent TRPV1 antagonist known to increase T_b of rats and mice and showed (by using knock-out mice) that the entire hyperthermic effect of AMG0347 is TRPV1 dependent. AMG0347-induced hyperthermia was brought about by one or both of the two major autonomic cold-defense effector mechanisms (tail-skin vasoconstriction and/or thermogenesis), but it did not involve warmth-seeking behavior. The magnitude of the hyperthermic response depended on neither T_b nor tail-skin temperature at the time of AMG0347 administration, thus indicating that AMG0347-induced hyperthermia results from blockade of tonic TRPV1 activation by nonthermal factors. AMG0347 was no more effective in causing hyperthermia when administered into the brain (intracerebroventricularly) or spinal cord (intrathecally) than when given systemically (intravenously), which indicates a peripheral site of action. We then established that localized intra-abdominal desensitization of TRPV1 channels with intraperitoneal resiniferatoxin blocks the T_b response to systemic AMG0347; the extent of desensitization was determined by using a comprehensive battery of functional tests. We conclude that tonic activation of TRPV1 channels in the abdominal viscera by yet unidentified nonthermal factors inhibits skin vasoconstriction and thermogenesis, thus having a suppressive effect on T_b .

The Journal of Neuroscience, July 11, 2007 • 27(28):7459–7468

Induction of Long-Term Memory by Exposure to Novelty Requires Protein Synthesis: Evidence for a Behavioral Tagging

Diego Moncada¹ and Haydée Viola^{1,2}

¹Instituto de Biología Celular y Neurociencias, Facultad de Medicina, and ²Departamento de Fisiología, Biología Molecular y Celular, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, 1121 Buenos Aires, Argentina

A behavioral analog of the synaptic tagging and capture process, a key property of synaptic plasticity, has been predicted recently. Here, we demonstrate that weak inhibitory avoidance training, which induces short- but not long-term memory (LTM), can be consolidated into LTM by an exploration to a novel, but not a familiar, environment occurring close in time to the training session. This memory-promoting effect caused by novelty depends on activation of dopamine D_1/D_5 receptors and requires newly synthesized proteins in the dorsal hippocampus. Thus, our results indicate the existence of a behavioral tagging process in which the exploration to a novel environment provides the plasticity-related proteins to stabilize the inhibitory avoidance memory trace.

The Journal of Neuroscience, July 11, 2007 • 27(28):7476–7481

Impact of Commitment on Performance Evaluation in the Rostral Cingulate Motor Area

Thomas Michelet, Bernard Bioulac, Dominique Guehl, Ludovic Escola, and Pierre Burbaud

Laboratoire de Physiologie et Physiopathologie de la Signalisation Cellulaire, Centre National de la Recherche Scientifique, Unité Mixte de Recherche 5543, Université Victor Segalen Bordeaux2, 33076 Bordeaux, France

Performance evaluation is a prerequisite for behavioral adaptation. Although the anterior cingulate cortex (ACC) is thought to play a central role in error detection, little is known about the electrophysiological activity of this structure during the performance-monitoring process. We directly addressed this issue by training monkeys to perform a Stroop-like task and then recorded neuronal activity in the rostral cingulate motor area (CMAR), a relatively unexplored region of the ACC known to be involved in motor processing. We found that most CMAR neurons responded during the evaluation period to both positive and negative feedback, but neuronal changes were more important after an error than after a successful trial. Interestingly, this performance-monitoring activity was not directly modulated by the degree of difficulty of the cognitive situation because changes in discharge frequency were similar whatever the level of attentional control imposed on the monkey. Firing activity during the evaluation period increased more, however, in erroneously completed than in incompleting trials and when the reward was delivered in an active rather than passive context, indicating that performance evaluation was conditioned by the degree of commitment of the animal to the task. It would thus seem that CMAR neurons could constitute a system for the evaluation of behavioral performance contingent on the subject's commitment to the task.

The Journal of Neuroscience, July 11, 2007 • 27(28):7482–7489

Psychophysical and Physiological Evidence for Parallel Afferent Pathways Mediating the Sensation of Itch

Lisa M. Johaneck,¹ Richard A. Meyer,^{1,3} Tim Hartke,¹ Joseph Greg Hobelmann,² David N. Maine,² Robert H. LaMotte,⁴ and Matthias Ringkamp¹

Departments of ¹Neurosurgery and ²Anesthesiology and ³The Applied Physics Laboratory, Johns Hopkins University, Baltimore, Maryland 21287, and

⁴Department of Anesthesiology, Yale, New Haven, Connecticut 06520

The neuronal pathways for itch have been characterized mainly based on responses to histamine. Intracutaneous application of histamine produces intense itch and a large area of axon-reflexive vasodilation (“flare”) around the application site. Both phenomena are thought to be mediated through neuronal activity in itch-specific, mechanoinsensitive C-fiber afferents (CMI). However, mechanical and electrical stimuli that do not activate CMI fibers can cause the sensation of itch, and itch may occur without flare, suggesting that other neuronal itch pathways exist. Because cutaneous application of spicules from the plant *Mucuna pruriens* (cowhage) has been anecdotally reported to produce itch without flare, we performed psychophysical experiments to investigate whether the mechanisms underlying cowhage- and histamine-induced itch differ. Although histamine and cowhage produced itch of similar magnitude, the itch to cowhage was not correlated with the itch to histamine; some subjects had intense itch to cowhage and little itch to histamine and visa versa. Laser Doppler measurements of blood flow revealed that histamine led to a large area of vasodilation, whereas cowhage produced vasodilation restricted to the application site. Pretreatment of the skin with an antihistamine blocked the itch produced by histamine but did not prevent cowhage-induced itch. Desensitization of the skin with topical capsaicin abolished cowhage-induced itch but did not significantly alter histamine-induced itch. These findings indicate that cowhage itch is signaled through a population of capsaicin-sensitive afferent nerve fibers that is distinct from CMI fibers mediating histamine-induced itch. Cowhage may be useful to investigate the neural pathway mediating nonhistaminergic itch.

The Journal of Neuroscience, July 11, 2007 • 27(28):7490–7497

Direct Instrumental Conditioning of Neural Activity Using Functional Magnetic Resonance Imaging-Derived Reward Feedback

Signe Bray,¹ Shinsuke Shimojo,^{1,2} and John P. O’Doherty^{1,3}

¹Computation and Neural Systems Program, ²Division of Biology, and ³Division of Humanities and Social Sciences, California Institute of Technology, Pasadena, California 91125

Successful learning is often contingent on feedback. In instrumental conditioning, an animal or human learns to perform specific responses to obtain reward. Instrumental conditioning is often used by behavioral psychologists to train an animal (or human) to produce a desired behavior. Shaping involves reinforcing those behaviors, which in a stepwise manner are successively closer to the desired behavior until the desired behavior is reached. Here, we aimed to extend this traditional approach to directly shape neural activity instead of overt behavior. To achieve this, we scanned 22 human subjects with functional magnetic resonance imaging and performed image processing in parallel with acquisition. We delineated regions of interest (ROIs) in finger and toe motor/somatosensory regions and used an instrumental shaping procedure to induce a regionally specific increase in activity by providing an explicit monetary reward to reinforce neural activity in the target areas. After training, we found a significant and regionally specific increase in activity in the ROI being rewarded (finger or toe) and a decrease in activity in the nonrewarded region. This demonstrates that instrumental conditioning procedures can be used to directly shape neural activity, even without the production of an overt behavioral response. This procedure offers an important alternative to traditional biofeedback-based approaches and may be useful in the development of future therapies for stroke and other brain disorders.

The Journal of Neuroscience, July 11, 2007 • 27(28):7498–7507

Chronic Mild Stress during Gestation Worsens Neonatal Brain Lesions in Mice

Claire-Marie Rangon,^{1,2*} Silvia Fortes,^{3*} Vincent Lelièvre,^{1,2} Philippe Leroux,⁴ Frank Plaisant,^{1,2} Chantal Joubert,³ Laurence Lanfumey,⁵ Charles Cohen-Salmon,^{3‡} and Pierre Gressens^{1,2,6‡}

¹Inserm, Unité 676, 75019 Paris, France, ²Université Paris 7, Faculté de Médecine Denis Diderot, Institut Fédératif de Recherche 02 (IFR02), 75005 Paris, France, ³Centre National de la Recherche Scientifique, Unité Mixte de Recherche 7593, Faculté de Médecine Pitié-Salpêtrière, 75634 Paris, France, ⁴Inserm, Avenir, IFR02, Faculté de Médecine et de Pharmacie, 76183 Rouen, France, ⁵Inserm, Unité 677, 75013 Paris, France, and ⁶Assistance Publique-Hôpitaux de Paris, Hôpital Robert Debré, Service de Neurologie Pédiatrique, 75019 Paris, France

Cerebral palsy remains a public health priority. Recognition of factors of susceptibility to perinatal brain lesions is key for the prevention of cerebral palsy. In most cases, the pathophysiology of these lesions is thought to involve prior exposure to predisposing factors that make the developing brain more vulnerable to perinatal events. The present study tested the hypothesis that exposure to chronic minimal stress throughout gestation would sensitize the offspring to neonatal excitotoxic brain lesions, which mimic lesions observed in cerebral palsy. Pregnant mice were exposed to chronic, ultramild stress, applied throughout gestation. Neonatal brain lesions were induced by intracerebral injection of glutamate analogs. Excitotoxic lesions were significantly worsened in pups exposed to gestational stress. Stress induced a significant rise of circulating corticosterone levels both in pregnant mothers and in newborn pups. The deleterious effects of stress on excitotoxicity were totally suppressed in mice with reduced levels of glucocorticoid receptors. Stress induced a significant increase of neopallial NMDA binding sites in the offspring. At adulthood, animals exposed to stress and neonatal excitotoxic challenge showed a significant impairment in the Morris water maze test when compared with animals exposed to the excitotoxic challenge but not the gestational stress. These findings suggest that stress during gestation, which may mimic low-level stress in human pregnancy, could be a novel risk factor for cerebral palsy.

The Journal of Neuroscience, July 11, 2007 • 27(28):7532–7540

Lesions of the Tegmentomammillary Circuit in the Head Direction System Disrupt the Head Direction Signal in the Anterior Thalamus

Joshua P. Bassett, Matthew L. Tullman, and Jeffrey S. Taube

Department of Psychological and Brain Sciences, Center for Cognitive Neuroscience, Dartmouth College, Hanover, New Hampshire 03755

Head direction (HD) cells in the rodent limbic system are believed to correspond to a cognitive representation of directional heading in the environment. Lesions of vestibular hair cells disrupt the characteristic firing patterns of HD cells, and thus vestibular afference is a critical contributor to the HD signal. A subcortical pathway that may convey this information includes the dorsal tegmental nucleus of Gudden (DTN) and the lateral mammillary nucleus (LMN). To test the hypothesis that the DTN and LMN are critical components for generating HD cell activity, we made electrolytic lesions of the DTN or LMN in rats and screened for HD cell activity in the anterior thalamus. Directional activity was absent in all animals with complete LMN lesions and in animals with complete DTN lesions, although a few HD cells were isolated in animals with incomplete lesions. Some DTN-lesioned animals contained cells whose firing rates were modulated by angular head velocity. Although cells with bursting patterns of activity have been observed in the anterior dorsal nucleus of the thalamus of animals with disruption of vestibular inputs, this pattern of activity was not observed in either the LMN- or DTN-lesioned animals. The general absence of direction-specific activity in the anterior thalamus of animals with DTN or LMN lesions is consistent with the view that the DTN–LMN circuit is essential for the generation of HD cell activity.

The Journal of Neuroscience, July 11, 2007 · 27(28):7564–7577

Neural Circuits Mediate Electrosensory Behavior in *Caenorhabditis elegans*

Christopher V. Gabel,¹ Harrison Gabel,^{2,3} Dmitri Pavlichin,¹ Albert Kao,¹ Damon A. Clark,¹ and Aravinthan D. T. Samuel¹

¹Department of Physics and Center for Brain Science, Harvard University, Cambridge, Massachusetts 02138, ²Department of Genetics, Harvard Medical School, and ³Department of Molecular Biology, Massachusetts General Hospital, Boston, Massachusetts 02114

The nematode *Caenorhabditis elegans* deliberately crawls toward the negative pole in an electric field. By quantifying the movements of individual worms navigating electric fields, we show that *C. elegans* prefers to crawl at specific angles to the direction of the electric field in persistent periods of forward movement and that the preferred angle is proportional to field strength. *C. elegans* reorients itself in response to time-varying electric fields by using sudden turns and reversals, standard reorientation maneuvers that *C. elegans* uses during other modes of motile behavior. Mutation or laser ablation that disrupts the structure and function of amphid sensory neurons also disrupts electrosensory behavior. By imaging intracellular calcium dynamics among the amphid sensory neurons of immobilized worms, we show that specific amphid sensory neurons are sensitive to the direction and strength of electric fields. We extend our analysis to the motor level by showing that specific interneurons affect the utilization of sudden turns and reversals during electrosensory steering. Thus, electrosensory behavior may be used as a model system for understanding how sensory inputs are transformed into motor outputs by the *C. elegans* nervous system.

The Journal of Neuroscience, July 11, 2007 · 27(28):7586–7596

A Novel Molecule “Shati” Is Involved in Methamphetamine-Induced Hyperlocomotion, Sensitization, and Conditioned Place Preference

Minae Niwa,^{1,3} Atsumi Nitta,¹ Hiroyuki Mizoguchi,¹ Yasutomo Ito,² Yukihiko Noda,¹ Taku Nagai,¹ and Toshitaka Nabeshima^{1,3}

¹Department of Neuropsychopharmacology and Hospital Pharmacy and ²Equipment Center for Research and Education, Nagoya University Graduate School of Medicine, Nagoya 466-8560, Japan, and ³Department of Chemical Pharmacology, Meijo University Graduate School of Pharmaceutical Sciences, Nagoya 468-8503, Japan

Drug addiction places an enormous burden on society through its repercussions on crime rate and healthcare. Repeated exposure to drugs of abuse causes cellular adaptations in specific neuronal populations that ultimately can lead to a state of addiction. In the present study, we have identified a novel molecule “shati” from the nucleus accumbens (NAc) of mice treated with methamphetamine (METH) using the PCR-select complementary DNA subtraction method. Moreover, we investigated whether shati is involved in METH-induced hyperlocomotion, sensitization, and conditioned place preference (CPP). METH induced expression of shati mRNA dose dependently via dopamine (DA) receptors. We prepared antibodies against shati and, using them, found shati to be expressed in neuronal cells of the mouse brain. Treatment with the shati antisense oligonucleotide (shati-AS), which significantly inhibited the expression of shati mRNA, enhanced the acute METH response, METH-induced behavioral sensitization, and CPP. Blockage of shati mRNA by shati-AS potentiated the METH-induced increase of DA overflow in the NAc and the METH-induced decrease in synaptosomal and vesicular DA uptake in the midbrain. These results suggest that a novel molecule shati is involved in the development of METH-induced hyperlocomotion, sensitization, and CPP. The functional roles of shati in METH-regulated behavioral alternations are likely to be mediated by its inhibitory effects on the METH-induced increase of DA overflow in the NAc and the METH-induced decrease in DA uptake in the midbrain.

The Journal of Neuroscience, July 11, 2007 · 27(28):7604–7615

Lymphotoxin β Receptor (Lt β R): Dual Roles in Demyelination and Remyelination and Successful Therapeutic Intervention Using Lt β R–Ig Protein

Sheila R. Plant,^{1,2*} Heather A. Iocca,^{1*} Ying Wang,¹ J. Cameron Thrash,⁴ Brian P. O'Connor,¹ Heather A. Arnett,^{1,2} Yang-Xin Fu,⁵ Monica J. Carson,⁴ and Jenny P.-Y. Ting^{1,2,3}

¹Lineberger Comprehensive Cancer Center, ²Neuroscience Center, and ³Department of Microbiology-Immunology, University of North Carolina, Chapel Hill, North Carolina 27599, ⁴Division of Biomedical Sciences, University of California, Riverside, California 92521, and ⁵Department of Pathology, The University of Chicago, Chicago, Illinois 60637

Inflammation mediated by macrophages is increasingly found to play a central role in diseases and disorders that affect a myriad of organs, prominent among these are diseases of the CNS. The neurotoxicant-induced, cuprizone model of demyelination is ideally suited for the analysis of inflammatory events. Demyelination on exposure to cuprizone is accompanied by predictable microglial activation and astrogliosis, and, after cuprizone withdrawal, this activation reproducibly diminishes during remyelination. This study demonstrates enhanced expression of lymphotoxin β receptor (Lt β R) during the demyelination phase of this model, and Lt β R is found in areas enriched with microglial and astroglial cells. Deletion of the Lt β R gene (Lt β R^{-/-}) resulted in a significant delay in demyelination but also a slight delay in remyelination. Inhibition of Lt β R signaling by an Lt β R–Ig fusion decoy protein successfully delayed demyelination in wild-type mice. Unexpectedly, this Lt β R–Ig decoy protein dramatically accelerated the rate of remyelination, even after the maximal pathological disease state had been reached. This strongly indicates the beneficial role of Lt β R–Ig in the delay of demyelination and the acceleration of remyelination. The discrepancy between remyelination rates in these systems could be attributed to developmental abnormalities in the immune systems of Lt β R^{-/-} mice. These findings bode well for the use of an inhibitory Lt β R–Ig as a candidate biological therapy in demyelinating disorders, because it is beneficial during both demyelination and remyelination.

The Journal of Neuroscience, July 11, 2007 • 27(28):7429–7437

Altered Localization of GABA_A Receptor Subunits on Dentate Granule Cell Dendrites Influences Tonic and Phasic Inhibition in a Mouse Model of Epilepsy

Nianhui Zhang,¹ Weizheng Wei,² Istvan Mody,^{2,3} and Carolyn R. Houser^{1,3,4}

Departments of ¹Neurobiology and ²Neurology and Physiology, and ³Brain Research Institute, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California 90095, and ⁴Research Service, Veterans Administration Greater Los Angeles Healthcare System, West Los Angeles, Los Angeles, California 90073

Complex changes in GABA_A receptors (GABA_ARs) in animal models of temporal lobe epilepsy during the chronic period include a decrease in the δ subunit and increases in the $\alpha 4$ and $\gamma 2$ subunits in the dentate gyrus. We used postembedding immunogold labeling to determine whether the subcellular locations of these subunits were also altered in pilocarpine-treated epileptic mice, and related functional changes were identified electrophysiologically. The ultrastructural studies confirmed a decrease in δ subunit labeling at perisynaptic locations in the molecular layer of the dentate gyrus where these subunits are critical for tonic inhibition. Unexpectedly, tonic inhibition in dentate granule cells was maintained in the epileptic mice, suggesting compensation by other GABA_ARs. An insensitivity of the tonic current to the neurosteroid tetrahydrodeoxy-corticosterone was consistent with decreased expression of the δ subunit. In the pilocarpine-treated mice, $\alpha 4$ subunit labeling remained at perisynaptic locations, but increased $\gamma 2$ subunit labeling was also found at many perisynaptic locations on granule cell dendrites, consistent with a shift of the $\gamma 2$ subunit from synaptic to perisynaptic locations and potential partnership of the $\alpha 4$ and $\gamma 2$ subunits in the epileptic animals. The decreased $\gamma 2$ labeling near the center of synaptic contacts was paralleled by a corresponding decrease in the dendritic phasic inhibition of granule cells in the pilocarpine-treated mice. These GABA_AR subunit changes appear to impair both tonic and phasic inhibition, particularly at granule cell dendrites, and could reduce the adaptive responses of the GABA system in temporal lobe epilepsy.

The Journal of Neuroscience, July 11, 2007 • 27(28):7520–7531