

This Week in The Journal

● Cellular/Molecular

Handling Synaptic Cargo in C. elegans

Sandhya P. Koushika, Anneliese M. Schaefer, Rose Vincent, John H. Willis, Bruce Bowerman, and Michael L. Nonet (see pages 3907–3916)

Trafficking of cargo between cell bodies and nerve cell processes involves both anterograde and retrograde transport using distinct molecular motors. Dynein, a microtubule motor protein involved in retrograde transport, performs its function as part of a complex with accessory proteins such as dynactin. Disruption of these complexes can produce features of motor neuron disease or amyotrophic lateral sclerosis (ALS). In this week's *Journal*, Koushika et al. identify *Caenorhabditis elegans* mutants in which retrograde vesicular transport runs afoul. They screened for defects in retrograde transport using GFP-tagged synaptobrevin as a marker. In the identified mutants, including a dynein light intermediate chain (*dli-1*) null mutant, synaptobrevin accumulated in distal neurites. These animals specifically failed to transport synaptobrevin and synaptotagmin but not other synaptic proteins. In addition to the accumulation of synaptic cargo, the worms developed progressive locomotor symptoms and died prematurely. These results illustrate the cargo specificity of retrograde transport and indicate that dynein dysfunction in *C. elegans* can mimic aspects of motor neuron disease.

▲ Development/Plasticity/Repair

Genes in Contextual Fear Conditioning

Jonathan M. Levenson, Sangdun Choi, Sun-Young Lee, Yun Anna Cao, Hyung Jin Ahn, Kim C. Worley, Marina Pizzi, Hsiou-Chi Liou, and J. David Sweatt (see pages 3933–3943)

It is now well accepted that consolidation of long-term memory (LTM) requires the synthesis of new mRNAs and proteins. But which genes are transcribed and translated, and when? This week, Levenson et al. screened 12,420 mouse genes for changes in expression in the CA1 and den-

tate region of the hippocampus during contextual fear conditioning, an NMDA receptor-dependent process. Of this total, 4000 genes had detectable hybridization signals in the examined regions. As might be expected, the authors' profiling identified dozens of regulated genes for which expression fluctuated in the hours after conditioning, including transcription factors, signaling molecules, and metabolic enzymes. Notably, the gene expression changes also required NMDA receptor activation. The authors focused in on one gene product, the transcription factor c-Rel, because a number of the memory consolidation-associated genes contained a c-Rel regulatory element. A null mutant c-Rel mouse could not form contextual memories, but associative memory was unaffected, confirming that c-Rel is necessary for hippocampal-dependent LTM.

■ Behavioral/Systems/Cognitive

Matching the Face with the Place

Charan Ranganath, Michael X. Cohen, Cathrine Dam, and Mark D'Esposito (see pages 3917–3925)

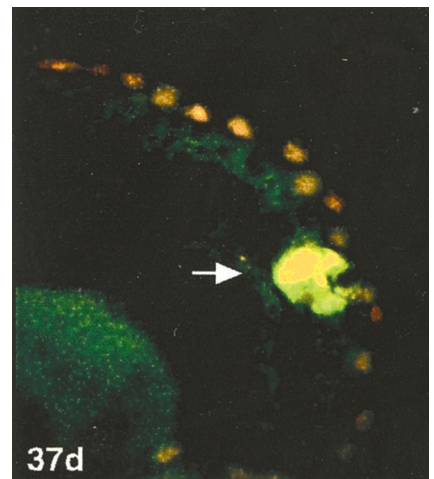
Goal-directed behavior depends on retrieving long-term memories as well as maintaining retrieved information in an active state. In this week's *Journal*, Ranganath et al. use functional magnetic resonance imaging to compare the cortical regions activated by a working memory task with those of an associative memory task. Subjects were trained to associate images of particular faces with particular houses, or were simply shown images of faces or houses alone. In a delayed match-to-sample test, subjects used working memory to hold a previously learned image in mind, while a delayed paired-association task required them to remember and recall a previously formed association. Category-specific areas of inferior temporal cortex lit up selectively; the fusiform face area (FFA) lit up when faces were the stimulus held in active memory, and the parahippocampal place area (PPA) lit up when houses were held in active memory. However, recall from long-term memory activated the anterior prefrontal cortex and hippocampus, providing evidence that these regions supply command signals for linking associative memory to behavioral tasks.

◆ Neurobiology of Disease

Alzheimer's in the Fly

Isabell Greeve, Doris Kretzschmar, Jakob-Andreas Tschäpe, Anika Beyn, Claire Brellinger, Michaela Schweizer, Roger M. Nitsch, and Rita Reifegerster (see pages 3899–3906)

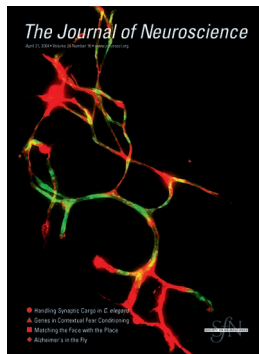
We generally think of Alzheimer's disease (AD) as a uniquely human disease marked by β -amyloid ($A\beta$) senile plaques and neurofibrillary tangles. However, as investigators close in on the involvement of key genes in AD, mouse models have played an increasingly vital role. Now Greeve et al. have manipulated these genes in *Drosophila* photoreceptor neurons to create a fly model of Alzheimer's-like amyloidosis. They used the GAL4/UAS system to express the human genes for amyloid precursor protein (APP) and the β -site APP-cleaving enzyme (BACE). The flies also express highly conserved homologs of presenilins 1 and 2 that further process APP. The fly neurons developed "star-like" $A\beta$ plaques similar to AD and showed photoreceptor degeneration that worsened with age and was reduced by disruption of γ -secretase activity. Ubiquitous expression of APP and BACE in the fly reduced viability. The *Drosophila* model supports a role for $A\beta$ in AD-induced neuronal death and provides a valuable additional tool for studies of AD pathogenesis and treatment.



Thioflavin S staining revealed amyloid plaques in the degenerated retina of *w; UAS-APP/+; UAS-DPsnL235P/gmr-GAL4* transgenic flies. See the article by Greeve et al. for details.

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Cover picture: The isolation of rat brain capillaries shows colocalization of the novel immediate early gene Verge (green) to endothelial cells (red). For details, see the article by Regard et al. in this issue (pages 4092–4103).

i This Week in The Journal

Brief Communications

4082 Intracellular Domains of a Rat Brain GABA Transporter That Govern Transport
Nina Hansra, Shruti Arya, and Michael W. Quick

4088 Acid-Sensing Ion Channel-2 Is Not Necessary for Sour Taste in Mice
Trevor A. Richter, Gennady A. Dvoryanchikov, Stephen D. Roper, and Nirupa Chaudhari

Articles

CELLULAR/MOLECULAR

3907 Mutations in *Caenorhabditis elegans* Cytoplasmic Dynein Components Reveal Specificity of Neuronal Retrograde Cargo
Sandhya P. Koushika, Anneliese M. Schaefer, Rose Vincent, John H. Willis, Bruce Bowerman, and Michael L. Nonet

3926 Differential Maturation of Climbing Fiber Innervation in Cerebellar Vermis
Hiroshi Nishiyama and David J. Linden

3964 Genetic Analysis of Soluble *N*-Ethylmaleimide-Sensitive Factor Attachment Protein Function in *Drosophila* Reveals Positive and Negative Secretory Roles
Michael Babcock, Greg T. Macleod, Jennifer Leither, and Leo Pallanck

3999 Voltage-Dependent Enhancement of Electrical Coupling by a Subthreshold Sodium Current
Sebastián Curti and Alberto E. Pereda

4030 Mice Lacking Sodium Channel β 1 Subunits Display Defects in Neuronal Excitability, Sodium Channel Expression, and Nodal Architecture
Chunling Chen, Ruth E. Westenbroek, Xiaorong Xu, Chris A. Edwards, Dorothy R. Sorenson, Yuan Chen, Dyke P. McEwen, Heather A. O'Malley, Vandana Bharucha, Laurence S. Meadows, Gabriel A. Knudsen, Alex Vilaythong, Jeffrey L. Noebels, Thomas L. Saunders, Todd Scheuer, Peter Shrager, William A. Catterall, and Lori L. Isom

4070 A Syntaxin 1, $G\alpha_s$, and N-Type Calcium Channel Complex at a Presynaptic Nerve Terminal: Analysis by Quantitative Immunocolocalization
Qi Li, Anthony Lau, Terence J. Morris, Lin Guo, Christopher B. Fordyce, and Elise F. Stanley

DEVELOPMENT/PLASTICITY/REPAIR

- 3933 **A Bioinformatics Analysis of Memory Consolidation Reveals Involvement of the Transcription Factor c-Rel**
Jonathan M. Levenson, Sangdun Choi, Sun-Young Lee, Yun Anna Cao, Hyung Jin Ahn, Kim C. Worley, Marina Pizzi, Hsiou-Chi Liou, and J. David Sweatt
- 3953 **Rho Kinase Regulates Schwann Cell Myelination and Formation of Associated Axonal Domains**
Carmen V. Melendez-Vasquez, Steven Einheber, and James L. Salzer
- 4092 **Verge: A Novel Vascular Early Response Gene**
Jean B. Regard, Sigrid Scheek, Talaipek Borbiev, Anthony A. Lanahan, Armin Schneider, Anna-Maria Demetriades, Holger Hiemisch, Carol A. Barnes, Alexander D. Verin, and Paul F. Worley

BEHAVIORAL/SYSTEMS/COGNITIVE

- 3917 **Inferior Temporal, Prefrontal, and Hippocampal Contributions to Visual Working Memory Maintenance and Associative Memory Retrieval**
Charan Ranganath, Michael X. Cohen, Cathrine Dam, and Mark D'Esposito
- 3944 **Maintenance of Spatial and Motor Codes during Oculomotor Delayed Response Tasks**
Clayton E. Curtis, Vikas Y. Rao, and Mark D'Esposito
- 3974 **Specific Na⁺ Sensors Are Functionally Expressed in a Neuronal Population of the Median Preoptic Nucleus of the Rat**
Magali Grob, Guy Drolet, and Didier Mougnot
- 3985 **Synaptic Responses to Whisker Deflections in Rat Barrel Cortex as a Function of Cortical Layer and Stimulus Intensity**
W. Bryan Wilent and Diego Contreras
- 4011 **Multiple Forms of Long-Term Potentiation and Long-Term Depression Converge on a Single Interneuron in the Leech CNS**
Brian D. Burrell and Christie L. Sahley
- 4020 **Corticotropin-Releasing Factor and Urocortin I Modulate Excitatory Glutamatergic Synaptic Transmission**
Jie Liu, Baojian Yu, Volker Neugebauer, Dimitri E. Grigoriadis, Jean Rivier, Wylie W. Vale, Patricia Shinnick-Gallagher, and Joel P. Gallagher
- 4061 **Optokinetic Deficits in Albino Ferrets (*Mustela putorius furo*): A Behavioral and Electrophysiological Study**
Klaus-Peter Hoffmann, Nicolaos Garipis, and Claudia Distler

NEUROBIOLOGY OF DISEASE

- 3899 **Age-Dependent Neurodegeneration and Alzheimer-Amyloid Plaque Formation in Transgenic *Drosophila***
Isabell Greeve, Doris Kretzschmar, Jakob-Andreas Tschäpe, Anika Beyn, Claire Brellinger, Michaela Schweizer, Roger M. Nitsch, and Rita Reifegerste
- 4043 **Transient Blockade of the CD11d/CD18 Integrin Reduces Secondary Damage after Spinal Cord Injury, Improving Sensory, Autonomic, and Motor Function**
Denis Gris, Daniel R. Marsh, Mark A. Oatway, Yuhua Chen, Eilis F. Hamilton, Gregory A. Dekaban, and Lynne C. Weaver
- 4052 **Dual Neuroprotective Signaling Mediated by Downregulating Two Distinct Phosphatase Activities of PTEN**
Ke Ning, Lin Pei, Mingxia Liao, Baosong Liu, Yunzhou Zhang, Wen Jiang, John G. Mielke, Lei Li, Yonghong Chen, Youssef H. El-Hayek, Michael G. Fehlings, Xia Zhang, Fang Liu, James Eubanks, and Qi Wan

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Brief Communications

Intracellular Domains of a Rat Brain GABA Transporter That Govern Transport

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Plasma membrane neurotransmitter transporters determine in part the concentration, time course, and diffusion of extracellular transmitter. Much has been learned about how substrate translocation through the transporter occurs; however, the precise way in which transporter structure maps onto transporter function has not yet been fully elucidated. Here, biochemical and electrophysiological approaches were used to test the hypothesis that intracellular domains of the rat brain GABA transporter (GAT1) contribute to the transport process. Injection of a peptide corresponding to the presumed fourth intracellular loop of the transporter (IL4) into oocytes expressing GAT1 greatly reduced both forward and reverse transport and reduced the transport rate in a dose-dependent manner. Coinjection of the IL4 peptide with a peptide corresponding to the N-terminal cytoplasmic tail of GAT1 reversed the IL4-mediated inhibition; this reversal, and direct binding between these two domains, was prevented by mutagenesis of charged residues in either the IL4 or N-terminal domains. Furthermore, syntaxin 1A, a soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) protein that inhibits GAT1 transport rates via interactions with the N-terminal tail of GAT1 was unable to regulate the GAT1 IL4 mutant. Together, these data suggest a model in which the GAT1 IL4 domain serves as a barrier for transport, and this barrier can be regulated through intra-molecular and inter-molecular interactions. *The Journal of Neuroscience*, April 21, 2004 • 24(16):4082–4087

Acid-Sensing Ion Channel-2 Is Not Necessary for Sour Taste in Mice

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The acid-sensitive cation channel acid-sensing ion channel-2 (ASIC2) is widely believed to be a receptor for acid (sour) taste in mammals on the basis of its physiological properties and expression in rat taste bud cells. Using reverse transcriptase-PCR, we detected expression of ASIC1 and ASIC3, but not ASIC4, in mouse and rat taste buds and nonsensory lingual epithelium. Surprisingly, we did not detect mRNA for ASIC2 in mouse taste buds, although we readily observed its expression in rat taste buds. Furthermore, in Ca^{2+} imaging experiments, ASIC2 knock-out mice exhibited normal physiological responses (increases in intracellular Ca^{2+} concentrations) to acid taste stimuli. Our results indicate that ASIC2 is not required for acid taste in mice, and that if a universal mammalian acid taste transduction mechanism exists, it likely uses other acid-sensitive receptors or ion channels.

The Journal of Neuroscience, April 21, 2004 • 24(16):4088–4091

Articles

CELLULAR/MOLECULAR

Mutations in *Caenorhabditis elegans* Cytoplasmic Dynein Components Reveal Specificity of Neuronal Retrograde Cargo

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We describe *Caenorhabditis elegans* dynein complex mutants, which misaccumulate synaptic proteins at the ends of neuronal processes. Ultrastructural analysis revealed irregularly sized vesicles that likely represent accumulation of cargo. We propose that synaptobrevin, synaptotagmin, and UNC-104 are specific cargoes of the dynein complex. Many cargoes link to dynein via interactions between dynactin and vesicle-associated spectrin. However, loss of spectrin results in only mild and occasional defects in synaptobrevin localization. Thus, the dynein–dynactin complex shows neuronal cargo selectivity without spectrin being a critical component of cargo binding. We observed parallels to progressive motor neuron disease symptoms in these animals. With age, neuronal misaccumulations increase in size and frequency; locomotion becomes progressively slower; and life span is shortened. These mutants provide a model to assess whether defects in transport of specific cargo mediate neuronal dysfunction.

The Journal of Neuroscience, April 21, 2004 • 24(16):3907–3916

Differential Maturation of Climbing Fiber Innervation in Cerebellar Vermis

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Folding of the brain surface is a general morphological adaptation to maximize surface area in a limited cranial volume. Surface folding is present not only in the neocortex but also in the cerebellar cortex. This folding creates subdivisions of the cortical surface: the sulci, the gyri, and the straight bank region, which is interposed. Is cortical folding only the solution to a surface–volume problem or does it also confer functional differences on the subdivisions that are created by this geometry? Here we have used the innervation of Purkinje cells by climbing fibers as a model system to explore potential functional differences. Purkinje cells are innervated by multiple climbing fibers at birth but undergo an activity-dependent refinement, such that by postnatal day (P) 21, most are contacted by a single climbing fiber. Using whole-cell recording from slices of cerebellar vermis derived from juvenile (P18–25) or adult (P60–83) mice, we found that significantly more Purkinje cells in the sulcus were innervated by multiple climbing fibers than in the gyrus or bank subdivisions; however, the basic properties of climbing fiber–Purkinje cell EPSCs such as kinetics, amplitude, and paired-pulse ratio were similar across cortical subdivisions. To search for a morphological correlate of differential multiple climbing fiber innervation, we labeled climbing fibers and performed reconstructions of immunofluorescent images. These revealed that, unlike the bank–gyrus subdivisions, most of the climbing fibers in the sulcus do not innervate the superficial molecular layer. These findings suggest that the subdivisions of the cerebellar cortex produced by folding may create functionally distinct entities. *The Journal of Neuroscience*, April 21, 2004 • 24(16):3926–3932

Genetic Analysis of Soluble *N*-Ethylmaleimide-Sensitive Factor Attachment Protein Function in *Drosophila* Reveals Positive and Negative Secretory Roles

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The *N*-ethylmaleimide-sensitive factor (NSF) and soluble NSF attachment protein (SNAP) are cytosolic factors that promote vesicle fusion with a target membrane in both the constitutive and regulated secretory pathways. NSF and SNAP are thought to function by catalyzing the disassembly of a SNAP receptor (SNARE) complex consisting of membrane proteins of the secretory vesicle and target membrane. Although studies of NSF function have provided strong support for this model, the precise biochemical role of SNAP remains controversial. To further explore the function of SNAP, we have used mutational and transgenic approaches in *Drosophila* to investigate the effect of altered SNAP dosage on neurotransmitter release and SNARE complex metabolism. Our results indicate that reduced SNAP activity results in diminished neurotransmitter release and accumulation of a neural SNARE complex. Increased SNAP dosage results in defective synapse formation and a variety of tissue morphological defects without detectably altering the abundance of neural SNARE complexes. The SNAP overexpression phenotypes are enhanced by mutations in other secretory components and are at least partially overcome by co-overexpression of NSF, suggesting that these phenotypes derive from a specific perturbation of the secretory pathway. Our results indicate that SNAP promotes neurotransmitter release and SNARE complex disassembly but inhibits secretion when present at high abundance relative to NSF. *The Journal of Neuroscience*, April 21, 2004 • 24(16):3964–3973

Voltage-Dependent Enhancement of Electrical Coupling by a Subthreshold Sodium Current

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Voltage-dependent changes in electrical coupling are often attributed to a direct effect on the properties of gap junction channels. Identifiable auditory afferents terminate as mixed (electrical and chemical) synapses on the distal portion of the lateral dendrite of the goldfish Mauthner cells, a pair of large reticulospinal neurons involved in the organization of sensory-evoked escape responses. At these afferents, the amplitude of the coupling potential produced by the retrograde spread of signals from the postsynaptic Mauthner cell is dramatically enhanced by depolarization of the presynaptic terminal. We demonstrate here that this voltage-dependent enhancement of electrical coupling does not represent a property of the junctions themselves but the activation of a subthreshold sodium current present at presynaptic terminals that acts to amplify the synaptic response. We also provide evidence that this amplification operates under physiological conditions, enhancing synaptic communication from the Mauthner cells to the auditory afferents where electrical and geometrical properties of the coupled cells are unfavorable for retrograde transmission. Retrograde electrical communication at these afferents may play an important functional role by promoting cooperativity between afferents and enhancing transmitter release. Thus, the efficacy of an electrical synapse can be dynamically modulated in a voltage-dependent manner by properties of the nonjunctional membrane. Finally, asymmetric amplification of electrical coupling by intrinsic membrane properties, as at the synapses between auditory afferents and the Mauthner cell, may ensure efficient communication between neuronal processes of dissimilar size and shape, promoting neuronal synchronization.

The Journal of Neuroscience, April 21, 2004 • 24(16):3999–4010

Mice Lacking Sodium Channel $\beta 1$ Subunits Display Defects in Neuronal Excitability, Sodium Channel Expression, and Nodal Architecture

Chunling Chen,¹ Ruth E. Westenbroek,⁴ Xiaorong Xu,⁵ Chris A. Edwards,² Dorothy R. Sorenson,² Yuan Chen,⁴ Dyke P. McEwen,¹ Heather A. O'Malley,¹ Vandana Bharucha,¹ Laurence S. Meadows,¹ Gabriel A. Knudsen,¹ Alex Vilaythong,⁶ Jeffrey L. Noebels,⁶ Thomas L. Saunders,³ Todd Scheuer,⁴ Peter Shrager,⁵ William A. Catterall,⁴ and Lori L. Isom¹

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Sodium channel $\beta 1$ subunits modulate α subunit gating and cell surface expression and participate in cell adhesive interactions *in vitro*. $\beta 1$ ($-/-$) mice appear ataxic and display spontaneous generalized seizures. In the optic nerve, the fastest components of the compound action potential are slowed and the number of mature nodes of Ranvier is reduced, but $\text{Na}_v1.6$, contactin, caspr 1, and K_v1 channels are all localized normally at nodes. At the ultrastructural level, the paranodal septate-like junctions immediately adjacent to the node are missing in a subset of axons, suggesting that $\beta 1$ may participate in axo-glia communication at the periphery of the nodal gap. Sodium currents in dissociated hippocampal neurons are normal, but $\text{Na}_v1.1$ expression is reduced and $\text{Na}_v1.3$ expression is increased in a subset of pyramidal neurons in the CA2/CA3 region, suggesting a basis for the epileptic phenotype. Our results show that $\beta 1$ subunits play important roles in the regulation of sodium channel density and localization, are involved in axo-glia communication at nodes of Ranvier, and are required for normal action potential conduction and control of excitability *in vivo*.

The Journal of Neuroscience, April 21, 2004 • 24(16):4030–4042

A Syntaxin 1, $G\alpha_o$, and N-Type Calcium Channel Complex at a Presynaptic Nerve Terminal: Analysis by Quantitative Immunocolocalization

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Presynaptic $\text{Ca}_v2.2$ (N-type) calcium channels are subject to modulation by interaction with syntaxin 1 and by a syntaxin 1-sensitive $G\alpha_o$ G-protein pathway. We used biochemical analysis of neuronal tissue lysates and a new quantitative test of colocalization by intensity correlation analysis at the giant calyx-type presynaptic terminal of the chick ciliary ganglion to explore the association of $\text{Ca}_v2.2$ with syntaxin 1 and $G\alpha_o$. $\text{Ca}_v2.2$ could be localized by immunocytochemistry (antibody Ab571) in puncta on the release site aspect of the presynaptic terminal and close to synaptic vesicle clouds. Syntaxin 1 coimmunoprecipitated with $\text{Ca}_v2.2$ from chick brain and chick ciliary ganglia and was widely distributed on the presynaptic terminal membrane. A fraction of the total syntaxin 1 colocalized with the $\text{Ca}_v2.2$ puncta, whereas the bulk colocalized with MUNC18-1. $G\alpha_o$, whether in its trimeric or monomeric state, did not coimmunoprecipitate with $\text{Ca}_v2.2$, MUNC18-1, or syntaxin 1. However, the G-protein exhibited a punctate staining on the calyx membrane with an intensity that varied in synchrony with that for both Ca channels and syntaxin 1 but only weakly with MUNC18-1. Thus, syntaxin 1 appears to be a component of two separate complexes at the presynaptic terminal, a minor one at the transmitter release site with $\text{Ca}_v2.2$ and $G\alpha_o$, as well as in large clusters remote from the release site with MUNC18-1. These syntaxin 1 protein complexes may play distinct roles in presynaptic biology.

The Journal of Neuroscience, April 21, 2004 • 24(16):4070–4081

DEVELOPMENT/PLASTICITY/REPAIR

A Bioinformatics Analysis of Memory Consolidation Reveals Involvement of the Transcription Factor *c-Rel*

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Consolidation of long-term memory (LTM) is a complex process requiring synthesis of new mRNAs and proteins. Many studies have characterized the requirement for *de novo* mRNA and protein synthesis; however, few studies have comprehensively identified genes regulated during LTM consolidation. We show that consolidation of long-term contextual memory in the hippocampus triggers altered expression of numerous genes encompassing many aspects of neuronal function. Like contextual memory formation, this altered gene expression required NMDA receptor activation and was specific for situations in which the animal formed an association between a physical context and a sensory stimulus. Using a bioinformatics approach, we found that regulatory elements for several transcription factors are over-represented in the upstream region of genes regulated during consolidation of LTM. Using a knock-out mouse, we found that *c-rel*, one of the transcription factors identified in our bioinformatics study, is necessary for hippocampus-dependent long-term memory formation.

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Rho Kinase Regulates Schwann Cell Myelination and Formation of Associated Axonal Domains

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The myelin sheath forms by the spiral wrapping of a glial membrane around an axon. The mechanisms involved are poorly understood but are likely to involve coordinated changes in the glial cell cytoskeleton. Because of its key role as a regulator of the cytoskeleton, we investigated the role of Rho kinase (ROCK), a major downstream effector of Rho, in Schwann cell morphology, differentiation, and myelination. Pharmacologic inhibition of ROCK activity results in loss of microvilli and stress fibers in Schwann cell cultures and strikingly aberrant myelination in Schwann cell–neuron cocultures; there was no effect on Schwann cell proliferation or differentiation. Treated Schwann cells branch aberrantly and form multiple, small, independent myelin segments along the length of axons, each with associated nodes and paranodes. This organization partially resembles myelin formed by oligodendrocytes rather than the single long myelin sheath characteristic of Schwann cells. ROCK regulates myosin light chain phosphorylation, which is robustly, but transiently, activated at the onset of myelination. These results support a key role of Rho through its effector ROCK in coordinating the movement of the glial membrane around the axon at the onset of myelination via regulation of myosin phosphorylation and actomyosin assembly. They also indicate that the molecular machinery that promotes the wrapping of the glial membrane sheath around the axon is distributed along the entire length of the internode.

The Journal of Neuroscience, April 21, 2004 • 24(16):3953–3963

Verge: A Novel Vascular Early Response Gene

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Vascular endothelium forms a continuous, semipermeable barrier that regulates the transvascular movement of hormones, macromolecules, and other solutes. Here, we describe a novel immediate early gene that is expressed selectively in vascular endothelial cells, *verge* (vascular early response gene). *Verge* protein includes an N-terminal region of ~70 amino acids with modest homology (~30% identity) to Apolipoprotein L but is otherwise unique. *Verge* mRNA and protein are induced selectively in the endothelium of adult vasculature by electrical or chemical seizures. *Verge* expression appears to be responsive to local tissue conditions, because it is induced in the hemisphere ipsilateral to transient focal cerebral ischemia. In contrast to the transient expression in adult, *Verge* mRNA and protein are constitutively expressed at high levels in the endothelium of developing tissues (particularly heart) in association with angiogenesis. *Verge* mRNA is induced in cultured endothelial cells by defined growth factors and hypoxia. *Verge* protein is dramatically increased by cysteine proteinase inhibitors, suggesting rapid turnover, and is localized to focal regions near the periphery of the cells. Endothelial cell lines that stably express *Verge* form monolayers that show enhanced permeability in response to activation of protein kinase C by phorbol esters. This response is accompanied by reorganization of the actin cytoskeleton and the formation of paracellular gaps. These studies suggest that *Verge* functions as a dynamic regulator of endothelial cell signaling and vascular function.

The Journal of Neuroscience, April 21, 2004 • 24(16):4092–4103

BEHAVIORAL/SYSTEMS/COGNITIVE

Inferior Temporal, Prefrontal, and Hippocampal Contributions to Visual Working Memory Maintenance and Associative Memory Retrieval

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Higher order cognition depends on the ability to recall information from memory and hold it in mind to guide future behavior. To specify the neural mechanisms underlying these processes, we used event-related functional magnetic resonance imaging to compare brain activity during the performance of a visual associative memory task and a visual working memory task. Activity within category-selective subregions of inferior temporal cortex reflected the type of information that was actively maintained during both the associative memory and working memory tasks. In addition, activity in the anterior prefrontal cortex and hippocampus was specifically enhanced during associative memory retrieval. These data are consistent with the view that the active maintenance of visual information is supported by activation of object representations in inferior temporal cortex, but that goal-directed associative memory retrieval additionally depends on top-down signals from the anterior prefrontal cortex and medial temporal lobes.

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Maintenance of Spatial and Motor Codes during Oculomotor Delayed Response Tasks

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The most compelling neural evidence for working memory is persistent neuronal activity bridging past sensory cues and their contingent future motor acts. This observation, however, does not answer what is actually being remembered or coded for by this activity. To address this fundamental issue, we imaged the human brain during maintenance of spatial locations and varied whether the memory-guided saccade was selected before or after the delay. An oculomotor delayed matching-to-sample task (match) was used to measure maintained motor intention because the direction of the forthcoming saccade was known throughout the delay. We used a nonmatching-to-sample task (nonmatch) in which the saccade was unpredictable to measure maintained spatial attention. Oculomotor areas were more active during match delays, and posterior parietal cortex and inferior frontal cortex were more active during nonmatch delays. Additionally, the fidelity of the memory was predicted by the delay-period activity of the frontal eye fields; the magnitude of delay-period activity correlated with the accuracy of the memory-guided saccade. Experimentally controlling response selection allowed us to functionally separate nodes of a network of frontal and parietal areas that usually coactivate in studies of working memory. We propose that different nodes in this network maintain different representational codes, motor and spatial. Which code is being represented by sustained neural activity is biased by when in the transformation from perception to action the response can be selected.

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Specific Na⁺ Sensors Are Functionally Expressed in a Neuronal Population of the Median Preoptic Nucleus of the Rat

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Whole-cell patch-clamp recordings were performed on acute brain slices of male rats to investigate the ability of the neurons of the median preoptic nucleus (MnPO) to detect fluctuation in extracellular osmolarity and sodium concentration ($[Na^+]_{out}$). Local application of hypotonic and hypertonic artificial CSF hyperpolarized and depolarized the neurons, respectively. Similar responses obtained under synaptic isolation (0.5 μM TTX) highlighted the intrinsic ability of the MnPO neurons to detect changes in extracellular osmolarity and $[Na^+]_{out}$. Manipulating extracellular osmolarity, $[Na^+]_{out}$, and $[Cl^-]_{out}$ showed in an independent manner that the MnPO neurons responded to a change in $[Na^+]_{out}$ exclusively. The specific Na⁺ response was voltage insensitive and depended on the driving force for Na⁺ ions, indicating that a sustained background Na⁺ permeability controlled the membrane potential of the MnPO neurons. This specific response was not reduced by Gd³⁺, amiloride, or benzamil, ruling out the participation of mechanosensitive cationic channels, specific epithelial Na⁺ channels, and Phe-Met-Arg-Phe-gated Na⁺ channels, respectively. Combination of *in situ* hybridization, using a riboprobe directed against the atypical Na⁺ channel (Na_x), and immunohistochemistry, using an antibody against neuron-specific nuclei protein, revealed that a substantial population of MnPO neurons expressed the Na_x channel, which was characterized recently as a concentration-sensitive Na⁺ channel. This study shows that a neuronal population of the MnPO acts as functional Na⁺ sensors and that the Na_x channel might represent the molecular basis for the extracellular sodium level sensing in these neurons.

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Synaptic Responses to Whisker Deflections in Rat Barrel Cortex as a Function of Cortical Layer and Stimulus Intensity

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To study the synaptic and spike responses of barrel cortex neurons as a function of cortical layer and stimulus intensity, we recorded intracellularly *in vivo* from barbiturate anesthetized rats while increasing the velocity–acceleration of the whisker deflection. Granular (Gr; layer 4) cells had the EPSP with the shortest peak and onset latency, whereas supragranular (SGr; layers 2–3) cells had the EPSP with longest duration and slowest rate of rise. Infragranular (Igr; layers 5–6) cells had intermediate values, and thus each layer was unique. The spike response peak of Gr cells was followed by IGr and then by SGr cells. In all cells, depolarization reduced the duration and amplitude of the response, but only in Gr cells did it reveal an early IPSP that cut short the EPSP. This early IPSP was associated with a large decrease in input resistance and an apparent reversal potential below spike threshold; consequently, synaptic integration in Gr cells was limited to the initial 5–7 msec of the response. In contrast, in SGr and IGr cells, results suggest an overlap in time of the EPSP and IPSP, with a small drop in input resistance and an apparent reversal potential above spike threshold, facilitating input integration for up to 20 msec. Decreasing stimulus intensity (velocity–acceleration) reduced the amplitude and increased the peak latency of the response without altering its synaptic composition. We propose that layer 4 circuits are better suited to perform coincidence detection, whereas supra and infragranular circuits are better designed for input integration.

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Multiple Forms of Long-Term Potentiation and Long-Term Depression Converge on a Single Interneuron in the Leech CNS

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Long-term potentiation (LTP) of synaptic transmission was observed in two types of synapses that converge on the same postsynaptic neuron in the leech CNS. These synapses were made by identifiable sensory neurons, the mechanosensory touch (T-) and pressure (P-) cells, onto the S-cell, an interneuron critical for certain forms of learning. Changes in both the T-S and P-S synapses appear to be activity dependent because LTP was restricted to inputs that had undergone tetanization; however, properties of synaptic plasticity at the T-S and P-S connections differ considerably. At the P-S synapse, LTP was induced in the tetanized synapse but not in the nontetanized synapse tested in parallel. P-S LTP was blocked by the NMDA receptor antagonist DL-2-amino-5-phosphono-valeric acid (AP-5) or by lowering the extracellular concentration of glycine, an NMDA receptor (NMDAR) co-agonist. P-S LTP was strongly affected by the initial amplitude of the synaptic potential at the time LTP was induced. Smaller amplitude synapses (<3.5 mV) underwent robust potentiation, whereas the less common, larger amplitude synapse (>3.5 mV) depressed after tetanization. At the T-S synapse, tetanization simultaneously induced homosynaptic LTP in the tetanized input and heterosynaptic long-term depression (LTD) in the input made by a nontetanized T-cell onto the same S-cell. Interestingly, AP-5 failed to block homosynaptic LTP at the T-S synapse but did prevent heterosynaptic LTD. T-S LTP was not affected by the initial EPSP amplitude. Thus, leech neurons exhibit synaptic plasticity with properties similar to LTP and LTD found in the vertebrate nervous system.

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Corticotropin-Releasing Factor and Urocortin I Modulate Excitatory Glutamatergic Synaptic Transmission

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Corticotropin-releasing factor (CRF)-related peptides serve as hormones and neuromodulators of the stress response and play a role in affective disorders. These peptides are known to alter complex behaviors and neuronal properties, but their receptor-mediated effects at CNS synapses are not well described. Here we show that excitatory glutamatergic transmission is modulated by two endogenous CRF-related peptide ligands, corticotropin-releasing factor [CRF rat/human (r/h)] and Urocortin I (Ucn I), within the central nucleus of the amygdala (CeA) and the lateral septum mediolateral nucleus (LSMLN). These limbic nuclei are reciprocally innervated, are involved in stress and affective disorders, and have high densities of the CRF receptors CRF₁ and CRF₂. Activation of these receptors exerts diametrically opposed actions on glutamatergic transmission in these nuclei. In the CeA, CRF(r/h) depressed excitatory glutamatergic transmission through a CRF₁-mediated postsynaptic action, whereas Ucn I facilitated synaptic responses through presynaptic and postsynaptic CRF₂-mediated mechanisms. Conversely, in the LSMLN, CRF caused a CRF₁-mediated facilitation of glutamatergic transmission via postsynaptic mechanisms, whereas Ucn I depressed EPSCs by postsynaptic and presynaptic CRF₂-mediated actions. Furthermore, antagonists of these receptors also affected glutamatergic neurotransmission, indicating that endogenous ligands tonically modulated synaptic activity at these synapses.

These data show that CRF receptors in CeA and LSMLN synapses exert and maintain a significant synaptic tone and thereby regulate excitatory glutamatergic transmission. The results also suggest that CRF receptors may provide novel targets in affective disorders and stress.

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Optokinetic Deficits in Albino Ferrets (*Mustela putorius furo*): A Behavioral and Electrophysiological Study

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We compared the horizontal optokinetic reaction (OKR) and response properties of retinal slip neurons in the nucleus of the optic tract and dorsal terminal nucleus (NOT-DTN) of albino and wild-type ferrets (*Mustela putorius furo*). In contrast to pigmented ferrets, we were unable to observe OKR in albino ferrets during binocular and monocular viewing using random dot full field stimulation and electro-oculography (EOG). Observations during early postnatal life indicate that regular OKR is present in pigmented pups 3 d after eye opening but is absent at any stage during development in albino ferrets. Unilateral muscimol injections to inactivate all neurons in the NOT-DTN containing GABA_A and GABA_C receptors caused spontaneous horizontal nystagmus with slow phases away from the injected hemisphere in albino as well as in pigmented animals. Retinal slip neurons in the NOT-DTN of albino ferrets identified by antidromic activation from the inferior olive and orthodromic activation from the optic chiasm were well responding to intermittent bright light stimuli, but many showed a profound reduction of responsiveness to moving stimuli. The movement-sensitive neurons exhibited no clear direction selectivity for ipsiversive stimulus movement, a characteristic property of these neurons in pigmented ferrets and other mammals. Thus, the defect rendering albino ferrets optokinetically nonresponsive is located in the visual pathway subserving the OKR, namely in or before the NOT-DTN, and not in oculomotor centers.

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Age-Dependent Neurodegeneration and Alzheimer-Amyloid Plaque Formation in Transgenic *Drosophila*

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β -Amyloid peptides that are cleaved from the amyloid precursor protein (APP) play a critical role in Alzheimer's disease (AD) pathophysiology. Here, we show that in *Drosophila*, the targeted expression of the key genes of AD, APP, the β -site APP-cleaving enzyme BACE, and the presenilins led to the generation of β -amyloid plaques and age-dependent neurodegeneration as well as to semilethality, a shortened life span, and defects in wing vein development. Genetic manipulations or pharmacological treatments with secretase inhibitors influenced the activity of the APP-processing proteases and modulated the severity of the phenotypes. This invertebrate model of amyloid plaque pathology demonstrates $A\beta$ -induced neurodegeneration as a basic biological principle and may allow additional genetic analyses of the underlying molecular pathways.

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Transient Blockade of the CD11d/CD18 Integrin Reduces Secondary Damage after Spinal Cord Injury, Improving Sensory, Autonomic, and Motor Function

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The early inflammatory response to spinal cord injury (SCI) causes significant secondary damage. Strategies that nonselectively suppress inflammation have not improved outcomes after SCI, perhaps because inflammation has both adverse and beneficial effects after SCI. We have shown that the selective, time-limited action of a monoclonal antibody (mAb) to the CD11d subunit of the CD11d/CD18 integrin, delivered intravenously during the first 48 hr after SCI in rats, markedly decreases the infiltration of neutrophils and delays the entry of hematogenous monocyte-macrophages into the injured cord. We hypothesized that this targeted strategy would lead to neuroprotection and improved neurological outcomes. In this study the development of chronic pain was detected in rats by assessing mechanical allodynia on the trunk and hindpaws 2 weeks to 3 months after a clinically relevant clip-compression SCI at the twelfth thoracic segment. The anti-CD11d mAb treatment reduced this pain by half. Motor performance also improved as rats were able to plantar-place their hindpaws and use them for weight support instead of sweeping movements only. Improved cardiovascular outcome was shown after SCI at the fourth thoracic segment by significant decreases in autonomic dysreflexia. Locomotor performance was also improved. These functional changes correlated with significantly greater amounts and increased organization of myelin and neurofilament near the lesion. The improved neurological recovery after the specific reduction of early inflammation after SCI demonstrates that this selective strategy increases tissue at the injury site and improves its functional capacity. This early neuroprotective treatment would be an ideal foundation for building later cell-based therapies.

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Dual Neuroprotective Signaling Mediated by Downregulating Two Distinct Phosphatase Activities of PTEN

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The tumor suppressor PTEN (phosphatase and tensin homolog deleted on chromosome 10) is a lipid and protein phosphatase. We report here that PTEN physically associates with the NR1 and NR2B subunits of NMDA receptors (NMDARs) in rat hippocampus. Downregulating the protein expression of PTEN inhibits the function of extrasynaptic NMDARs and decreases NMDAR surface expression, suggesting a crucial role for endogenous PTEN in the modulation of NMDAR-mediated neuronal function. Reducing PTEN expression also enhances Akt/Bad phosphorylation in hippocampal neurons. Importantly, suppressing lipid and protein phosphatase activity of PTEN, respectively, activates Akt and inhibits extrasynaptic NMDAR activity and thereby protects against ischemic neuronal death *in vitro* and *in vivo*. Thus, our study reveals a dual neuroprotective mechanism by which Akt/Bad and extrasynaptic NMDARs are regulated via downregulation of two distinct PTEN phosphatase activities and present the possibility of PTEN as a potential therapeutic target for stroke treatment.

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