This Week in The Journal

● Cellular/Molecular

Adding Membranes to Synapses

David Gorczyca, James Ashley, Sean Speese, Norberto Gherbesi, Ulrich Thomas, Eckart Gundelfinger, L. Sian Gramates, and Vivian Budnik

(see pages 1033–1044)

Nothing is a more fundamental operation than addition, even when it comes to synaptic membranes. This week, Gorczyca et al. addressed the complex process of targeted membrane addition at the larval *Drosophila* neuromuscular junction, particularly the specialized, multilayered postsynaptic membrane called the subsynaptic reticulum (SSR). The authors used the guanylate kinase-like domain of the fly scaffolding protein Discs-Large (DLG) as bait in a yeast two-hybrid screen. They isolated guanylate kinase-interacting syntaxin [Gtaxin (GTX)]. GTX colocalized with DLG at postsynaptic glutamatergic type I boutons but not at type II and III boutons. GTX and DLG interacted *in vivo*, and targeting of GTX to the SSR depended on DLG. Like *dlg* mutants, *gtx* mutants exhibited a severely compromised SSR. Overexpression of GTX resulted in the formation of extrasynaptic SSR-like structures independent of DLG, indicating a role for GTX in membrane addition.

▲ Development/Plasticity/Repair

Drosophila Cacophony Channels

I-Feng Peng and Chun-Fang Wu

(see pages 1072–1081)

In the second of three papers using *Drosophila* in This Week in the Journal, Peng and Wu cataloged the diverse properties of calcium channel currents encoded by the *cacophony* (*cac*) locus. The authors made whole-cell voltage-clamp and current-clamp recordings from cultured "giant" neurons, generated from fly embryo cells in which cytokinesis had been halted. Recordings from neurons in wild-type and two *cac* mutants, cac^{s} and cac^{ts2}, showed that *cac* currents varied in their kinetics, displaying low- and high-voltage activation and both fast and slow inactivation. Interestingly, the currents were sensitive to T-type but not L-type calcium channel blockers. Calcium entry through *cac*-encoded channels was required for calcium-activated potassium current ($I_{K(Ca)}$). In *cac* mutant neurons, the inactivating potassium current I_A was upregulated, an effect mimicked by chronic pharmacological block of *cac* channels, apparently attributable to upregulation of *Shaker* (*Sh*) potassium channels.

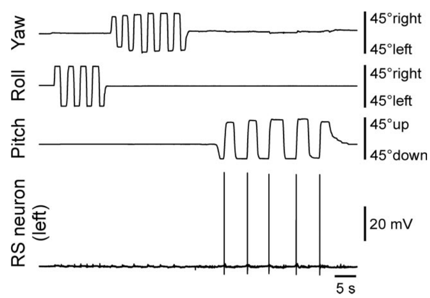
■ Behavioral/Systems/Cognitive

Roll, Pitch, and Yaw, Lamprey-Style

Pavel V. Zelenin, Grigori N. Orlovsky, and Tatiana G. Deliagina

(see pages 1024–1032)

Steering a lamprey through the murky depths presents some of the same engineering control issues that face airplane pilots. This week, Zelenin et al. examined the control system of the lamprey that maintains body orientation in the sagittal (pitch), transversal (roll), and horizontal (yaw) planes. Brainstem reticulospinal (RS) neurons receive vestibular inputs and send outputs to the motoneuron pools to maintain body orientation. The authors used an *in vitro* preparation in which the brainstem, vestibular organs, and rostral spinal cord were dissected en bloc along with the cranium and notochord. The notochord was attached to the chamber, and the cranium was attached to a plate that rotated around three axes. The authors made intracellular recordings from RS neurons, and recorded motoneuron responses with surface electrodes. In each plane, RS neurons responded to rotations in one of two opposing directions. Each RS group drove motoneurons that led to a corrective movement.



The response of an RS neuron that responded only to stabilization of the pitch angle. See the article by Zelenin et al. for details.

♦ Neurobiology of Disease

A Fly Model of Parkin-Induced PD

Tzu-Kang Sang, Hui-Yun Chang, George M. Lawless, Anuradha Ratnaparkhi, Lisa Mee, Larry C. Ackerson, Nigel T. Maidment, David E. Krantz, and George R. Jackson

(see pages 981–992)

Although most cases of Parkinson's disease (PD) are sporadic, mutations in parkin underlie an autosomal recessive juvenile form as well as some adult cases. This week, Sang et al. used a *Drosophila* model system to test whether parkin mutations and dopamine co-conspire to cause the selective vulnerability of dopaminergic neurons. The authors expressed human wild-type parkin ($parkin^{wt}$) or familial PD parkin mutants ($parkin^{T240R}$ and $parkin^{Q311X}$) in fly aminergic neurons under control of a *DOPA decarboxylase* (*ddc*)-GAL4 driver. Immediately after eclosion, all flies performed equally well on tests of motor function, but by 4 weeks, flies expressing mutant parkin were severely impaired, and DA neurons were specifically and progressively reduced. Overexpression of the DVMAT (*Drosophila* vesicular monoamine transporter), which controls cytosolic levels of DA, rescued flies from the mutant parkin phenotype. The idea is that dopamine oxidation leads to modification of parkin, particularly mutant forms, reducing its E3 ligase activity and increasing susceptibility to cell toxicity.

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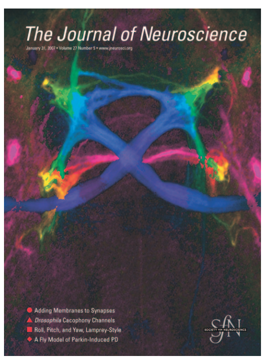

Cover legend: A high-powered view of the optic chiasm of a 72 h zebrafish larva that is mutant for the axonal guidance receptor robo2. Loss of robo2 makes retinal axons insensitive to slits, repellents that help guide them across the midline and to their targets. Anterior is to the top, and the eyes are out of frame on either side. Retinal axons are color coded depending on their dorsal–ventral position in the brain, with cool colors indicating ventral levels near the chiasm and warm colors indicating more dorsal levels. Retinal axons sweep towards the center, cross at the ventral midline, travel to the contralateral side of the brain, and then extend dorsally. A variety of profound axonal pathfinding errors can be seen, including ectopic retinal commissures at both ventral and dorsal levels. This projection image was made on a Leica DMIRE2 confocal microscope of a fish in which retinal axons were visualized by GFP expression driven by the Brn3C promoter (a kind gift from the Baier laboratory, University of California, San Francisco). For more information, see the article by Chalasani et al. in this issue (pages 973–980).

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BRIEF COMMUNICATIONS

The Critical Role of Locomotion Mechanics in Decoding Sensory Systems

Noah J. Cowan[1] **and Eric S. Fortune**[2]
Departments of [1]Mechanical Engineering and [2]Psychological and Brain Sciences, Johns Hopkins University, Baltimore, Maryland 21218

How do neural systems process sensory information to control locomotion? The weakly electric knifefish *Eigenmannia*, an ideal model for studying sensorimotor control, swims to stabilize the sensory image of a sinusoidally moving refuge. Tracking performance is best at stimulus frequencies less than ~1 Hz. Kinematic analysis, which is widely used in the study of neural control of movement, predicts commensurately low-pass sensory processing for control. The inclusion of Newtonian mechanics in the analysis of the behavior, however, categorically shifts the prediction: this analysis predicts that sensory processing is high pass. The counterintuitive prediction that a low-pass behavior is controlled by a high-pass neural filter nevertheless matches previously reported but poorly understood high-pass filtering seen in electrosensory afferents and downstream neurons. Furthermore, a model incorporating the high-pass controller matches animal behavior, whereas the model with the low-pass controller does not and is unstable. Because locomotor mechanics are similar in a wide array of animals, these data suggest that such high-pass sensory filters may be a general mechanism used for task-level locomotion control. Furthermore, these data highlight the critical role of mechanical analyses in addition to widely used kinematic analyses in the study of neural control systems.
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Acute Hypoxia Activates the Neuroimmune System, Which Diabetes Exacerbates

Daniel R. Johnson,[1] **Jason C. O'Connor,**[2] **Matthew E. Hartman,**[1] **Richard I. Tapping,**[3] **and Gregory G. Freund**[1,2,4]
[1]Department of Animal Sciences, [2]Division of Nutritional Science, [3]Department of Medical Microbiology, and [4]Department of Pathology, Integrative Immunology and Behavior Program, University of Illinois, Urbana, Illinois 61801

Acute hypoxia is experienced in an array of ailments and conditions, including asthma, chronic obstructive pulmonary disease, heart failure, sleep apnea, acute hypotension, and blast lung injury. Classically, infection activates the neuroimmune system, causing loss of interest in the social environment. We report that the non-infectious stimulus acute hypoxia triggers neuroimmune system activation (NSA), causing loss of interest in the social environment, and that recovery from hypoxia-induced NSA is impaired in a mouse model of type 2 diabetes. Importantly, recovery from the behavioral consequences of hypoxia-induced NSA was nearly ablated in MyD88 (myeloid differentiation factor 88) knock-out mice and in mice intracerebroventricularly administered the caspase-1 inhibitor ac-YVAD-CMK (ac-Tyr-Val-Asp-2,6-dimethylbenzoyloxymethylketone). Diabetic mice had prolonged recovery from NSA that could be halved by administration of subcutaneous interleukin-1 (IL-1) receptor antagonist (RA). These results show that acute hypoxia activates the IL-1β arm of the neuroimmune system, which diabetes exacerbates and treatment with IL-1RA ameliorates.
The Journal of Neuroscience, January 31, 2007 • 27(5):1161–1166

Signaling at A-Kinase Anchoring Proteins Organizes Anesthesia-Sensitive Memory in *Drosophila*

Martin Schwaerzel, Andrea Jaeckel, and Uli Mueller
Saarland University, Faculty 8.3 Life Science, Department of Zoology and Physiology, 66041 Saarbrucken, Germany

The ubiquitous cAMP–protein kinase A (PKA) signaling pathway exhibits complex temporal requirements during the time course of associative memory processing. This directly raises questions about the molecular mechanisms that provide signaling specificity to this pathway. Here, we use *Drosophila* olfactory conditioning to show that divergent cAMP signaling is mediated by functionally distinct pools of PKA. One particular pool is organized via the PKA regulatory type II subunit at the level of A-kinase anchoring proteins (AKAPs), a family of scaffolding proteins that provides focal points of spatiotemporal signal integration. This AKAP-bound pool of PKA is acting within neurons of the mushroom bodies to support a late phase of aversive memory. The requirement for AKAP-bound PKA signaling is limited to aversive memory, but dispensable during appetitive memory. This finding suggests the existence of additional mechanisms to support divergence within the cAMP–PKA signaling pathway during memory processing. Together, our results show that subcellular organization of signaling components plays a key role in memory processing.
The Journal of Neuroscience, January 31, 2007 • 27(5):1229–1233

Articles

CELLULAR/MOLECULAR

Mechanoelectric Transduction of Adult Inner Hair Cells

Shuping Jia,[1] **Peter Dallos,**[2] **and David Z. Z. He**[1]
[1]Hair Cell Biophysics Laboratory, Department of Biomedical Sciences, Creighton University School of Medicine, Omaha, Nebraska 68178, and [2]Auditory Physiology Laboratory, The Hugh Knowles Center, Departments of Neurobiology and Physiology, and Communication Sciences and Disorders, Northwestern University, Evanston, Illinois 60208

Inner hair cells (IHCs) are the true sensory receptors in the cochlea; they transmit auditory information to the brain. IHCs respond to basilar membrane (BM) vibration by producing a transducer current through mechanotransducer (MET) channels located at the tip of their stereocilia when these are deflected. The IHC MET current has not

been measured from adult animals. We simultaneously recorded IHC transducer currents and BM motion in a gerbil hemicochlea to examine relationships between these two variables and their variation along the cochlear length. Results show that although maximum transducer currents of IHCs are uniform along the cochlea, their operating range is graded and is narrower in the base. The MET current displays adaptation, which along with response magnitude depends on extracellular calcium concentration. The rate of adaptation is invariant along the cochlear length. We introduce a new method of measuring adaptation using sinusoidal stimuli. There is a phase lead of IHC transducer currents relative to sinusoidal BM displacement, reflecting viscoelastic coupling of their cilia and their adaptation process.
The Journal of Neuroscience, January 31, 2007 • 27(5):1006–1014

Postsynaptic Membrane Addition Depends on the Discs-Large-Interacting t-SNARE Gtaxin

David Gorczyca,[1]* James Ashley,[1]* Sean Speese,[1] Norberto Gherbesi,[1] Ulrich Thomas,[2] Eckart Gundelfinger,[2] L. Sian Gramates,[3] and Vivian Budnik[1]

[1]Department of Neurobiology, University of Massachusetts Medical School, Worcester, Massachusetts 01605, [2]Leibniz Institute for Neurobiology, 39118 Magdeburg, Germany, and [3]Molecular and Cellular Biology Graduate Program, University of Massachusetts at Amherst, Amherst, Massachusetts 01003

Targeted membrane addition is a hallmark of many cellular functions. In the nervous system, modification of synaptic membrane size has a major impact on synaptic function. However, because of the complex shape of neurons and the need to target membrane addition to very small and polarized synaptic compartments, this process is poorly understood. Here, we show that Gtaxin (GTX), a *Drosophila* t-SNARE (target-soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor), is required for expansion of postsynaptic membranes during new synapse formation. Mutations in *gtx* lead to drastic reductions in postsynaptic membrane surface, whereas *gtx* upregulation results in the formation of complex membrane structures at ectopic sites. Postsynaptic GTX activity depends on its direct interaction with Discs-Large (DLG), a multidomain scaffolding protein of the PSD-95 (postsynaptic density protein-95) family with key roles in cell polarity and formation of cellular junctions as well as synaptic protein anchoring and trafficking. We show that DLG selectively determines the postsynaptic distribution of GTX to type I, but not to type II or type III boutons on the same cell, thereby defining sites of membrane addition to this unique set of glutamatergic synapses. We provide a mechanistic explanation for selective targeted membrane expansion at specific synaptic junctions.
The Journal of Neuroscience, January 31, 2007 • 27(5):1033–1044

Progressive Loss of Dopaminergic Neurons in the Ventral Midbrain of Adult Mice Heterozygote for *Engrailed1*

Laure Sonnier,[1]* Gwenaëlle Le Pen,[2]* Andreas Hartmann,[3] Jean-Charles Bizot,[4] Fabrice Trovero,[4] Marie-Odile Krebs,[2] and Alain Prochiantz[1]

[1]Centre National de la Recherche Scientifique, Unité Mixte de Recherche 8542, Development and Evolution of the Nervous System, Group Development and Neuropharmacology, Ecole Normale Supérieure, 75230 Paris Cedex 05, France, [2]Institut National de la Santé et de la Recherche Médicale, Unit 796, Pathophysiology of Psychiatric Disorders, University Paris Descartes, Faculty of Medicine Paris Descartes, Sainte-Anne Hospital, Paris F-75014, France, [3]Institut National de la Santé et de la Recherche Médicale, Unit 679, Neurology and Experimental Therapeutics, Hospital of Pitié-Salpêtrière and University Pierre and Marie Curie, Faculty of Medicine, Paris 75013, France, and [4]Keyobs, Centre d'Innovation, 45100 Orléans Cedex 2, France

Engrailed1 and *Engrailed2* (*En1* and *En2*) are two developmental genes of the homeogene family expressed in the developing midbrain. *En1* and, to a lesser degree, *En2* also are expressed in the adult substantia nigra (SN) and ventral tegmental area (VTA), two dopaminergic (DA) nuclei of the ventral midbrain. In an effort to study *En1/2* adult functions, we have analyzed the phenotype of mice lacking one *En1* allele in an *En2* wild-type context. We show that in this mutant the number of DA neurons decreases slowly between 8 and 24 weeks after birth to reach a stable 38 and 23% reduction in the SN and VTA, respectively, and that neuronal loss can be antagonized by En2 recombinant protein infusions in the midbrain. These loss and gain of function experiments firmly establish that *En1/2* is a true survival factor for DA neurons *in vivo*. Neuronal death in the mutant is paralleled by a 37% decrease in striatal DA, with no change in serotonin content. Using established protocols, we show that, compared with their wild-type littermates, *En1+/−* mice have impaired motor skills, an anhedonic-like behavior, and an enhanced resignation phenotype; they perform poorly in social interactions. However, these mice do not differ from their wild-type littermates in anxiety-measuring tests. Together, these results demonstrate that *En1/2* genes have important adult physiological functions. They also suggest that mice lacking only one *En1* allele could provide a novel model for the study of diseases associated with progressive DA cell death.
The Journal of Neuroscience, January 31, 2007 • 27(5):1063–1071

The Role of Muscle Activation Pattern and Calcineurin in Acetylcholinesterase Regulation in Rat Skeletal Muscles

Peter Pregelj,[1]* Miha Trinkaus,[1]* Daša Zupan,[1] Jože J. Trontelj,[2] and Janez Sketelj[1]

[1]Institute of Pathophysiology, Faculty of Medicine, University of Ljubljana, and [2]Institute of Clinical Neurophysiology, Clinical Center, SI-1000 Ljubljana, Slovenia

Acetylcholinesterase (AChE) expression in fast rat muscles is approximately fourfold higher than in slow muscles. We examined whether different muscle activation patterns are responsible for this difference and whether the calcineurin signaling pathway is involved in AChE regulation. The slow soleus and fast extensor digitorum longus (EDL) muscles were directly or indirectly stimulated by a tonic low-frequency or a phasic high-frequency pattern of electric impulses. The phasic, but not tonic, stimulation increased the AChE mRNA levels in denervated soleus muscles to those in the normal EDL and maintained high levels of AChE mRNA in denervated EDL muscles. Therefore, muscle activation pattern is the predominant regulator of extrajunctional AChE expression in rat muscles. Indirect phasic stimulation of innervated muscles, imposed on their natural pattern of neural activation, did not increase the AChE transcript levels in the soleus, whereas a 30% reduction was observed in the EDL

muscles. A low number of impulses per day is therefore prerequisite for high AChE expression. Treatment by tacrolimus and cyclosporin A, two inhibitors of calcineurin (but not by a related substance rapamycin, which does not inhibit calcineurin), increased the levels of AChE transcripts in the control soleus muscles and in tonically electrically stimulated soleus and EDL muscles, even to reach those in the control EDL muscles. Therefore, tonic muscle activation reduces the extrajunctional levels of AChE transcripts by activating the calcineurin signaling pathway. In denervated soleus and EDL muscles, tacrolimus did not prevent the reduction of AChE mRNA levels, indicating that a calcineurin-independent suppressive mechanism was involved.
The Journal of Neuroscience, January 31, 2007 • 27(5):1106–1113

Three Distinct Mechanisms Generate Oxygen Free Radicals in Neurons and Contribute to Cell Death during Anoxia and Reoxygenation

Andrey Y. Abramov,[1] Antonella Scorziello,[2] and Michael R. Duchen[1]
[1]Department of Physiology, University College London, London WC1E 6BT, United Kingdom, and [2]Department of Neuroscience, University of Naples Federico II, 80131 Naples, Italy

Ischemia is a major cause of brain damage, and patient management is complicated by the paradoxical injury that results from reoxygenation. We have now explored the generation of reactive oxygen species (ROS) in hippocampal and cortical neurons in culture in response to oxygen and glucose deprivation or metabolic inhibition and reoxygenation. Fluorescence microscopy was used to measure the rate of ROS generation using hydroethidine, dicarboxyfluorescein diacetate, or MitoSOX. ROS generation was correlated with changing mitochondrial potential (rhodamine 123), $[Ca^{2+}]_c$ (fluo-4, fura-2, or Indo-1), or ATP consumption, indicated by increased $[Mg^{2+}]_c$. We found that three distinct mechanisms contribute to neuronal injury by generating ROS and oxidative stress, each operating at a different stage of ischemia and reperfusion. In response to hypoxia, mitochondria generate an initial burst of ROS, which is curtailed once mitochondria depolarize or prevented by previous depolarization with uncoupler. A second phase of ROS generation that followed after a delay was blocked by the xanthine oxidase (XO) inhibitor oxypurinol. This phase correlated with a rise in $[Mg^{2+}]_c$, suggesting XO activation by accumulating products of ATP consumption. A third phase of ROS generation appeared at reoxygenation. This was blocked by NADPH oxidase inhibitors and was absent in cells from gp91 $^{phox-/-}$ knock-out mice. It was Ca^{2+} dependent, suggesting activation by increased $[Ca^{2+}]_c$ during anoxia, itself partly attributable to glutamate release. Inhibition of either the NADPH oxidase or XO was significantly neuroprotective. Thus, oxidative stress contributes to cell death over and above the injury attributable to energy deprivation.
The Journal of Neuroscience, January 31, 2007 • 27(5):1129–1138

Transducin Translocation in Rods Is Triggered by Saturation of the GTPase-Activating Complex

Ekaterina S. Lobanova,[1] Stella Finkelstein,[1] Hongman Song,[2] Stephen H. Tsang,[3] Ching-Kang Chen,[4] Maxim Sokolov,[5] Nikolai P. Skiba,[1] and Vadim Y. Arshavsky[1]
[1]Albert Eye Research Institute, Duke University Medical Center, Durham, North Carolina 27710, [2]Department of Biochemistry, West Virginia University School of Medicine, Morgantown, West Virginia 26506, [3]Brown Glaucoma Laboratory, Edward Harkness Eye Institute, Columbia University, New York, New York 10032, [4]Department of Biochemistry, Virginia Commonwealth University, Richmond, Virginia 23298, and [5]Sensory Neuroscience Research Center and West Virginia University Eye Institute, Morgantown, West Virginia 26506

Light causes massive translocation of G-protein transducin from the light-sensitive outer segment compartment of the rod photoreceptor cell. Remarkably, significant translocation is observed only when the light intensity exceeds a critical threshold level. We addressed the nature of this threshold using a series of mutant mice and found that the threshold can be shifted to either a lower or higher light intensity, dependent on whether the ability of the GTPase-activating complex to inactivate GTP-bound transducin is decreased or increased. We also demonstrated that the threshold is not dependent on cellular signaling downstream from transducin. Finally, we showed that the extent of transducin α subunit translocation is affected by the hydrophobicity of its acyl modification. This implies that interactions with membranes impose a limitation on transducin translocation. Our data suggest that transducin translocation is triggered when the cell exhausts its capacity to activate transducin GTPase, and a portion of transducin remains active for a sufficient time to dissociate from membranes and to escape from the outer segment. Overall, the threshold marks the switch of the rod from the highly light-sensitive mode of operation required under limited lighting conditions to the less-sensitive energy-saving mode beneficial in bright light, when vision is dominated by cones.
The Journal of Neuroscience, January 31, 2007 • 27(5):1151–1160

Regulation of Postsynaptic Ca^{2+} Influx in Hippocampal CA1 Pyramidal Neurons via Extracellular Carbonic Anhydrase

Nataliya Fedirko, Marat Avshalumov, Margaret E. Rice, and Mitchell Chesler
Department of Neurosurgery and Department of Physiology and Neuroscience, New York University School of Medicine, New York, New York 10016

Synchronous neural activity causes rapid changes of extracellular pH (pH_e) in the nervous system. In the CA1 region of the hippocampus, stimulation of the Schaffer collaterals elicits an alkaline pH_e transient in stratum radiatum that is limited by extracellular carbonic anhydrase (ECA). When interstitial buffering is diminished by inhibition of ECA, the alkalosis is enhanced and NMDA receptor (NMDAR)-mediated postsynaptic currents can be augmented. Accordingly, the dendritic influx of Ca^{2+} elicited by synaptic excitation may be expected to increase if ECA activity were blocked. We tested this hypothesis in the CA1 stratum radiatum of hippocampal slices from juvenile rats, using extracellular, concentric pH- and Ca^{2+}-selective microelectrodes with response times of a few milliseconds, as well as Fluo-5F imaging of intracellular Ca^{2+} transients. Brief stimulation of the Schaffer collaterals elicited an alkaline pH_e transient, a transient decrease in free extracellular Ca^{2+} concentration ($[Ca^{2+}]_e$), and a corresponding transient rise in free intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$). Inhibition of ECA with benzolamide caused a marked amplification and prolonged

recovery of the pH_e and $[Ca^{2+}]_e$ responses, as well as the dendritic $[Ca^{2+}]_i$ transients. The increase in amplitude caused by benzolamide did not occur in the presence of the NMDAR antagonist APV, but the decay of the responses was still prolonged. These results indicate that ECA can shape dendritic Ca^{2+} dynamics governed by NMDARs by virtue of its regulation of concomitant activity-dependent pH_e shifts. The data also suggest that Ca^{2+} transients are influenced by additional mechanisms sensitive to shifts in pH_e.
The Journal of Neuroscience, January 31, 2007 • 27(5):1167–1175

Munc13-1 C1 Domain Activation Lowers the Energy Barrier for Synaptic Vesicle Fusion

Jayeeta Basu,[1] Andrea Betz,[2] Nils Brose,[2] and Christian Rosenmund[1]

[1]Departments of Neuroscience and Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas 77030, and [2]Max-Planck-Institute for Experimental Medicine, Department of Molecular Neurobiology, D-37075 Göttingen, Germany

Synapses need to encode a wide dynamic range of action potential frequencies. Essential vesicle priming proteins of the Munc13 (mammalian Unc13) family play an important role in adapting vesicle supply to variable demand and thus influence short-term plasticity characteristics and synaptic function. Structure–function analyses of Munc13s have identified a "catalytic" C-terminal domain and several N-terminal modulatory domains, including a diacylglycerol/phorbol ester [4β-phorbol-12, 13-dibutyrate (PDBu)] binding C1 domain. Although still allowing basal priming, a Munc13-1 C1 domain mutation (H567K) prevents PDBu induced potentiation of evoked transmitter release, leads to strong depression during trains of synaptic activity, and causes perinatal lethality in mice. To understand the mechanism of C1 domain-mediated modulation of Munc13 function, we examined how PDBu increases neurotransmitter release. Analyses of osmotically induced release as well as Ca^{2+} triggered and spontaneous release showed that PDBu increases the vesicular release rate without affecting the size of the readily releasable vesicle pool, linking C1 domain activation to a lowering of the energy barrier for vesicle fusion. PDBu binding-deficient mutant Munc13-1^{H567K} synapses mirrored the vesicular release properties of PDBu-potentiated wild-type synapses, indicating that Munc13-1^{H567K} is a gain-of-function mutant, which conformationally mimics the PDBu-activated state of Munc13-1. We propose a PKC analogous two-state model of regulation of Munc13s, in which the basal state of Munc13s is disinhibited by C1 domain activation into a state of facilitated vesicle release, regardless of whether the release is spontaneous or action potential triggered.
The Journal of Neuroscience, January 31, 2007 • 27(5):1200–1210

Presynaptic Monoacylglycerol Lipase Activity Determines Basal Endocannabinoid Tone and Terminates Retrograde Endocannabinoid Signaling in the Hippocampus

Yuki Hashimotodani,[1] Takako Ohno-Shosaku,[3] and Masanobu Kano[2]

Departments of [1]Neurophysiology and [2]Cellular Neuroscience, Graduate School of Medicine, Osaka University, Suita 565-0871, Japan, and [3]Department of Impairment Study, Graduate School of Medical Science, Kanazawa University, Kanazawa 920-0942, Japan

Endocannabinoids function as retrograde messengers and modulate synaptic transmission through presynaptic cannabinoid CB1 receptors. The magnitude and time course of endocannabinoid signaling are thought to depend on the balance between the production and degradation of endocannabinoids. The major endocannabinoid 2-arachidonoylglycerol (2-AG) is hydrolyzed by monoacylglycerol lipase (MGL), which is shown to be localized at axon terminals. In the present study, we investigated how MGL regulates endocannabinoid signaling and influences synaptic transmission in the hippocampus. We found that MGL inhibitors, methyl arachidonoyl fluorophosphonate and arachidonoyl trifluoromethylketone, caused a gradual suppression of cannabinoid-sensitive IPSCs in cultured hippocampal neurons. This suppression was reversed by blocking CB1 receptors and was attenuated by inhibiting 2-AG synthesis, indicating that MGL scavenges constitutively released 2-AG. We also found that the MGL inhibitors significantly prolonged the suppression of both IPSCs and EPSCs induced by exogenous 2-AG and depolarization-induced suppression of inhibition/excitation, a phenomenon known to be mediated by retrograde endocannabinoid signaling. In contrast, inhibitors of other endocannabinoid hydrolyzing enzymes, fatty acid amide hydrolase and cyclooxygenase-2, had no effect on the 2-AG-induced IPSC suppression. These results strongly suggest that presynaptic MGL not only hydrolyzes 2-AG released from activated postsynaptic neurons but also contributes to degradation of constitutively produced 2-AG and prevention of its accumulation around presynaptic terminals. Thus, the MGL activity determines basal endocannabinoid tone and terminates retrograde endocannabinoid signaling in the hippocampus.
The Journal of Neuroscience, January 31, 2007 • 27(5):1211–1219

DEVELOPMENT/PLASTICITY/REPAIR

Stromal Cell-Derived Factor-1 Antagonizes Slit/Robo Signaling *In Vivo*

Sreekanth H. Chalasani,[1]* Angela Sabol,[1]* Hong Xu,[1] Michael A. Gyda,[2] Kendall Rasband,[3] Michael Granato,[2] Chi-Bin Chien,[3] and Jonathan A. Raper[1]

[1]Neuroscience Department and [2]Cell and Developmental Biology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104, and [3]Department of Neurobiology and Anatomy, University of Utah Medical Center, Salt Lake City, Utah 84132

Retinal ganglion cell axons exit the eye, enter the optic stalk, cross the ventral midline at the optic chiasm, and terminate in the optic tectum of the zebrafish. While in the optic stalk, they grow immediately adjacent to cells expressing the powerful retinal axon repellent slit2. The chemokine stromal cell-derived factor-1 (SDF1) is expressed within the optic stalk and its receptor CXCR4 is expressed in retinal ganglion cells. SDF1 makes cultured retinal axons less responsive to slit2. Here, we show that reducing SDF1 signaling *in vivo* rescues retinal axon pathfinding errors in zebrafish mutants that have a partial functional loss of the slit receptor robo2. In contrast, reducing SDF1

signaling in animals that completely lack the robo2 receptor does not rescue retinal guidance errors. These results demonstrate that endogenous levels of SDF1 antagonize the repellent effects of slit/robo signaling *in vivo* and that this antagonism is important during axonal pathfinding.
The Journal of Neuroscience, January 31, 2007 • 27(5):973–980

Neurophysiological Mechanisms Involved in Transfer of Procedural Knowledge

Monica A. Perez,[1] Steven P. Wise,[2] Daniel T. Willingham,[3] and Leonardo G. Cohen[1]
[1]Human Cortical Physiology Section, National Institute of Neurological Disorders and Stroke and [2]Laboratory of Systems Neuroscience, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland 20892, and [3]Department of Psychology, University of Virginia, Charlottesville, Virginia 22904

Learning to perform a motor task with one hand results in performance improvements in the other hand, a process called intermanual transfer. To gain information on its neural mechanisms, we studied this phenomenon using the serial reaction-time task (SRTT). Sixteen, right-handed volunteers trained a 12-item sequence of key presses repeated without the subjects' knowledge. Blocks with no repeating sequence, called random blocks, were interspersed with sequence-training blocks. Response times improved in random and training blocks in both hands. The former result reflects nonspecific improvement in performance, and the latter represents a sequence-specific improvement. To evaluate changes in the primary motor cortex (M1), we tested resting motor thresholds (RMT), recruitments curves to transcranial magnetic stimulation (RC), short intracortical inhibition (SICI), and interhemispheric inhibition (IHI) from the dominant left (learning) to the nondominant right (transfer) hemisphere, before and after SRTT training. Training resulted in (1) increased RC and decreased SICI but no changes in RMT in the learning hemisphere, (2) decreased SICI and no changes in RC or RMT in the transfer hemisphere, and (3) decreased IHI. The amount in IHI after training correlated with nonspecific performance improvements in the transfer hand but not with sequence-specific performance improvements. Our results indicate that modulation of interhemispheric inhibition between the M1 areas may, as a result of the learning that has occurred in one hemisphere after practice with one hand, contribute to faster, more skilled performance of the opposite hand.
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DEVELOPMENTAL/PLASTICITY/REPAIR

Drosophila cacophony Channels: A Major Mediator of Neuronal Ca^{2+} Currents and a Trigger for K^+ Channel Homeostatic Regulation

I-Feng Peng and Chun-Fang Wu
Department of Biological Sciences, University of Iowa, Iowa City, Iowa 52242

The *cacophony* (*cac*) locus in *Drosophila* encodes a Ca^{2+} channel α subunit, but little is known about properties of *cac*-mediated currents and functional consequences of *cac* mutations in central neurons. We found that, in *Drosophila* cultured neurons, Ca^{2+} currents were mediated predominantly by the *cac* channels. The *cac* channels contribute to low- and high-threshold, fast- and slow-inactivating types of Ca^{2+} currents, take part in membrane depolarization, and strongly activate Ca^{2+}-activated K^+ current [$I_{K(Ca)}$]. In *cac* neurons, unexpectedly, voltage-activated transient K^+ current I_A is upregulated to a level that matches $I_{K(Ca)}$ reduction, implicating a homeostatic regulation that was mimicked by chronic pharmacological blockade of Ca^{2+} currents in wild-type neurons. Among K^+ channel transcripts, *Shaker* mRNA levels were preferentially increased in *cac* flies. However, Ca^{2+} current expression levels remained unaltered in several K^+ channel mutants, illustrating a key role of *cac* in developmental regulation of *Drosophila* neuronal excitability.
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DEVELOPMENT/PLASTICITY/REPAIR

Endogenous Brain-Derived Neurotrophic Factor Triggers Fast Calcium Transients at Synapses in Developing Dendrites

Susanne B. Lang, Valentin Stein, Tobias Bonhoeffer, and Christian Lohmann
Max Planck Institute of Neurobiology, 82152 Martinsried-München, Germany
Brain-derived neurotrophic factor (BDNF) is involved in many aspects of the formation of functional neuronal networks. BDNF signaling regulates neuronal development not only globally, at the level of entire neurons or networks, but also at a subcellular level and with high temporal specificity; however, the spatiotemporal characteristics of intrinsic BDNF signaling are essentially unknown. Here, we used calcium imaging to directly observe intrinsic BDNF signaling in developing hippocampal neurons. We found that blocking intrinsic BDNF signaling with function-blocking BDNF antibodies (αBDNF) or K252-a reduced the frequency of spontaneously occurring fast and localized calcium rises in dendrites. Conversely, focal application of BDNF evoked fast and local dendritic calcium transients, which required activation of TrkB (tropomyosin-related kinase B) receptors as well as activation of voltage-gated sodium and calcium channels. Virus-mediated expression of PSD-95:CFP (postsynaptic density-95 tagged with cyan fluorescent protein) revealed that spontaneous local calcium transients occurred frequently at postsynaptic sites along the dendrite. The frequency of synaptically localized calcium transients was specifically reduced by blocking intrinsic BDNF signaling, whereas nonsynaptic calcium rises were not affected. Furthermore, focal BDNF delivery evoked localized and fast calcium elevations specifically at postsynaptic sites. Together, our results demonstrate that BDNF-dependent calcium signaling in developing hippocampal neurons is fast and occurs at synapses. These temporal and spatial characteristics of intrinsic BDNF signaling as well as its relative abundance renders BDNF an ideal signaling molecule in the establishment of specific synaptic connectivity and functional neuronal networks.
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Impaired Axonal Regeneration by Isolectin B4-Binding Dorsal Root Ganglion Neurons *In Vitro*

Pascal G. Leclere,[1] Emma Norman,[1] Filitsa Groutsi,[2] Robert Coffin,[2] Ulrike Mayer,[3] John Pizzey,[1] and David Tonge[1]

[1]The Wolfson Centre for Age Related Diseases, School of Biomedical and Health Sciences, King's College London, London SE1 1UL, United Kingdom, [2]Department of Immunology and Molecular Pathology, University College London, London W1T 4JF, United Kingdom, and [3]Biomedical Research Centre, School of Biological Sciences, University of East Anglia, Norwich NR14 7TJ, United Kingdom

The subpopulation of dorsal root ganglion (DRG) neurons recognized by *Griffonia simplicifolia* isolectin B4 (IB4) differ from other neurons by expressing receptors for glial cell line-derived neurotrophic factor (GDNF) rather than neurotrophins. Additionally, IB4-labeled neurons do not express the laminin receptor, α7-integrin (Gardiner et al., 2005), necessary for optimal axonal regeneration in the peripheral nervous system. In cultures of dissociated DRG neurons of adult mice on laminin, robust spontaneous neurite outgrowth from IB4-negative neurons occurs and is strongly enhanced by previous axotomy. In contrast, IB4-labeled neurons show little neurite outgrowth and do not express GAP 43, even after axotomy or culture with GDNF. Moreover, growth of their axons through collagen gels is impaired compared with other DRG neurons. To determine whether the sparse neurite outgrowth of IB4-labeled neurons is attributable to lack of integrin expression, DRG cultures were infected with a herpes simplex 1 vector encoding α7-integrin, but its forced expression failed to promote neurite outgrowth in either IB4-labeled or other DRG neurons or in cultured adult retinal ganglion cells. Forced coexpression of both α7-integrin and GAP 43 also failed to promote neurite outgrowth in IB4-labeled neurons. In addition, cultured sciatic nerve segments were found to release much lower levels of GDNF, demonstrated by ELISA, than nerve growth factor. These findings together with their impaired intrinsic axonal regeneration capacity may contribute to the known vulnerability of the IB4-labeled population of DRG neurons to peripheral nerve injury.

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BEHAVIORAL/SYSTEMS/COGNITIVE

$P2Y_1$ Receptor Modulation of the Pre-Bötzinger Complex Inspiratory Rhythm Generating Network *In Vitro*

Amanda R. Lorier,[1,2] Adrianne G. Huxtable,[1] Dean M. Robinson,[2] Janusz Lipski,[2] Gary D. Housley,[2] and Gregory D. Funk[1,2]

[1]Department of Physiology, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada T6G 2H7, and [2]Department of Physiology, Faculty of Medicine and Health Sciences, University of Auckland, Auckland, Private Bag 92019, New Zealand

ATP is released during hypoxia from the ventrolateral medulla (VLM) and activates purinergic P2 receptors (P2Rs) at unknown loci to offset the secondary hypoxic depression of breathing. In this study, we used rhythmically active medullary slices from neonatal rat to map, in relation to anatomical and molecular markers of the pre-Bötzinger complex (preBötC) (a proposed site of rhythm generation), the effects of ATP on respiratory rhythm and identify the P2R subtypes responsible for these actions. Unilateral microinjections of ATP in a three-dimensional grid within the VLM revealed a "hotspot" where ATP (0.1 mM) evoked a rapid 2.2 $\pm$ 0.1-fold increase in inspiratory frequency followed by a brief reduction to 0.83 $\pm$ 0.02 of baseline. The hotspot was identified as the preBötC based on histology, overlap of injection sites with NK1R immunolabeling, and potentiation or inhibition of respiratory frequency by SP ([Sar^9-Met(O$_2$)^{11}]-substance P) or DAMGO ([D-Ala^2,*N*-MePhe^4,Gly-ol^5]-enkephalin), respectively. The relative potency of P2R agonists [2MeSADP (2-methylthioadenosine 5′-diphosphate) $\approx$ 2MeSATP (2-methylthioadenosine 5′-triphosphate) $\approx$ ATPγs (adenosine 5′-[γ-thio]triphosphate tetralithium salt) $\approx$ ATP $\gg$ UTP $\approx$ $\alpha\beta$meATP (α,β-methylene-adenosine 5′-triphosphate)] and attenuation of the ATP response by MRS2179 (2′-deoxy-*N*^{6}-methyladenosine-3′,5′-bisphosphate) ($P2Y_1$ antagonist) indicate that the excitation is mediated by $P2Y_1$Rs. The post-ATP inhibition, which was never observed in response to ATPγs, is dependent on ATP hydrolysis. These data establish in neonatal rats that respiratory rhythm generating networks in the preBötC are exquisitely sensitive to $P2Y_1$R activation, and suggest a role for $P2Y_1$Rs in respiratory motor control, particularly in the P2R excitation of rhythm that occurs during hypoxia.

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Visual Cortex Allows Prediction of Perceptual States during Ambiguous Structure-From-Motion

Gijs Joost Brouwer and Raymond van Ee

Helmholtz Institute, University of Utrecht, 3584 CC Utrecht, The Netherlands

We investigated the role of retinotopic visual cortex and motion-sensitive areas in representing the content of visual awareness during ambiguous structure-from-motion (SFM), using functional magnetic resonance imaging (fMRI) and multivariate statistics (support vector machines). Our results indicate that prediction of perceptual states can be very accurate for data taken from dorsal visual areas V3A, V4D, V7, and MT+ and for parietal areas responsive to SFM, but to a lesser extent for other visual areas. Generalization of prediction was possible, because prediction accuracy was significantly better than chance for both an unambiguous stimulus and a different experimental design. Detailed analysis of eye movements revealed that strategic and even encouraged beneficial eye movements were not the cause of the prediction accuracy based on cortical activation. We conclude that during perceptual rivalry, neural correlates of visual awareness can be found in retinotopic visual cortex, MT+, and parietal cortex. We argue that the organization of specific motion-sensitive neurons creates detectable biases in the preferred direction selectivity of voxels, allowing prediction of perceptual states. During perceptual rivalry, retinotopic visual cortex, in particular higher-tier dorsal areas like V3A and V7, actively represents the content the visual awareness.

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Sensory-Motor Transformation by Individual Command Neurons

Pavel V. Zelenin, Grigori N. Orlovsky, and Tatiana G. Deliagina
The Nobel Institute for Neurophysiology, Department of Neuroscience, Karolinska Institute, SE-171 77 Stockholm, Sweden

Animals and humans maintain a definite body orientation in space during locomotion. Here we analyze the system for the control of body orientation in the lamprey (a lower vertebrate). In the swimming lamprey, commands for changing the body orientation are based on vestibular information; they are transmitted to the spinal cord by reticulospinal (RS) neurons. The aim of this study was to characterize the sensory-motor transformation performed by individual RS neurons. The brainstem–spinal cord preparation with vestibular organs was used. For each RS neuron, we recorded (1) its vestibular responses to turns in different planes and (2) responses in different motoneuron pools of the spinal cord to stimulation of the same RS neuron; the latter data allowed us to estimate the direction of torque (caused by the RS neuron) that will rotate the animal's body during swimming. For each of the three main planes (roll, pitch, and yaw), two groups of RS neurons were found; they were activated by rotation in opposite directions and caused the torques counteracting the rotation that activated the neuron. In each plane, the system will stabilize the orientation at which the two groups are equally active; any deviation from this orientation will evoke a corrective motor response. Thus, individual RS neurons transform sensory information about the body orientation into the motor commands that cause corrections of orientation. The closed-loop mechanisms formed by individual neurons of a group operate in parallel to generate the resulting motor responses.
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Selective Bilateral Amygdala Lesions in Rhesus Monkeys Fail to Disrupt Object Reversal Learning

Alicia Izquierdo and Elisabeth A. Murray
Section on the Neurobiology of Learning and Memory, Laboratory of Neuropsychology, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland 20892

Neuropsychological studies in nonhuman primates have led to the view that the amygdala plays an essential role in stimulus–reward association. The main evidence in support of this idea is that bilateral aspirative or radiofrequency lesions of the amygdala yield severe impairments on object reversal learning, a task that assesses the ability to shift choices of objects based on the presence or absence of food reward (i.e., reward contingency). The behavioral effects of different lesion techniques, however, can vary. The present study therefore evaluated the effects of selective, excitotoxic lesions of the amygdala in rhesus monkeys on object reversal learning. For comparison, we tested the same monkeys on a task known to be sensitive to amygdala damage, the reinforcer devaluation task. Contrary to previous results based on less selective lesion techniques, monkeys with complete excitotoxic amygdala lesions performed object reversal learning as quickly as controls. As predicted, however, the same operated monkeys were impaired in making object choices after devaluation of the associated food reinforcer. The results suggest two conclusions. First, the results demonstrate that the amygdala makes a selective contribution to stimulus–reward association; the amygdala is critical for guiding object choices after changes in reward value but not after changes in reward contingency. Second, the results implicate a critical contribution to object reversal learning of structures nearby the amygdala, perhaps the subjacent rhinal cortex.
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Selective Visual Attention to Emotion

Harald T. Schupp,[1] Jessica Stockburger,[1] Maurizio Codispoti,[2] Markus Junghöfer,[3] Almut I. Weike,[4] and Alfons O. Hamm[4]
[1]Department of Psychology, University of Konstanz, 78457 Konstanz, Germany, [2]Department of Psychology, University of Bologna, 40127 Bologna, Italy, [3]Institute for Biomagnetism and Biosignalanalysis, University of Münster, 48149 Münster, Germany, and [4]Department of Psychology, University of Greifswald, 17487 Greifswald, Germany

Visual attention can be voluntarily directed toward stimuli and is attracted by stimuli that are emotionally significant. The present study explored the case when both processes coincide and attention is directed to emotional stimuli. Participants viewed a rapid and continuous stream of high-arousing erotica and mutilation stimuli as well as low-arousing control images. Each of the three stimulus categories served in separate runs as target or nontarget category. Event-related brain potential measures revealed that the interaction of attention and emotion varied for specific processing stages. The effects of attention and emotional significance operated additively during perceptual encoding indexed by negative-going potentials over posterior regions (∼200–350 ms after stimulus onset). In contrast, thought to reflect the process of stimulus evaluation, P3 target effects (∼400–600 ms after stimulus onset) were markedly augmented when erotica and mutilation compared with control stimuli were the focus of attention. Thus, emotion potentiated attention effects specifically during later stages of processing. These findings suggest to specify the interaction of attention and emotion in distinct processing stages.
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What You See Is Not (Always) What You Hear: Induced Gamma Band Responses Reflect Cross-Modal Interactions in Familiar Object Recognition

Shlomit Yuval-Greenberg[1] **and Leon Y. Deouell**[1,2]

[1]Department of Psychology, and [2]Interdisciplinary Center for Neural Computation, The Hebrew University of Jerusalem, Jerusalem 91905, Israel

Gamma-band responses (GBRs) are hypothesized to reflect neuronal synchronous activity related to activation of object representations. However, it is not known whether synchrony in the gamma range is also related to multisensory object processing. We investigated the effect of semantic congruity between auditory and visual information on the human GBR. The paradigm consisted of a simultaneous presentation of pictures and vocalizations of animals, which were either congruent or incongruent. EEG was measured in 17 students while they attended either the auditory or the visual stimulus and performed a recognition task. Behavioral results showed a congruity effect, indicating that information from the unattended modality affected behavior. Irrelevant visual information affected auditory recognition more than irrelevant auditory information affected visual recognition, suggesting a bias toward reliance on visual information in object recognition. Whereas the evoked (phase-locked) GBR was unaffected by congruity, the induced (non-phase-locked) GBR was increased for congruent compared with incongruent stimuli. This effect was independent of the attended modality. The results show that integration of information across modalities, based on semantic congruity, is associated with enhanced synchronized oscillations at the gamma band. This suggests that gamma-band oscillations are related not only to low-level unimodal integration but also to the formation of object representations at conceptual multisensory levels.

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Plasticity in Brain Sexuality Is Revealed by the Rapid Actions of Steroid Hormones

Luke Remage-Healey and Andrew H. Bass

Department of Neurobiology and Behavior, Cornell University, Ithaca, New York 14853

Divergent steroid hormone profiles can shape the development of male versus female neural phenotypes, but whether they also determine differences in the short-term, neurophysiological patterning of behavior is unknown. We now show that steroid hormone-specific modulation of a vocal pattern generator (VPG) diverges between reproductive morphs in a teleost fish. Only type I male midshipman acoustically court females, whereas type II males steal fertilizations from type I males and, like females, generate only agonistic calls. The androgen 11-ketotestosterone (11kT), but not testosterone (T), rapidly (within 5 min) increases type I VPG output. As now shown, T, but not 11kT, rapidly increases VPG output in type II males and females, consistent with the predominant circulating androgen in type II males and females (T) versus type Is (11kT). Receptor and enzyme antagonists reveal an unexpected divergence in androgen- versus estrogen-dependent mechanisms in, respectively, type II males versus females. Cortisol, the main circulating glucocorticoid, also has divergent actions: suppressing versus increasing VPG output in, respectively, type II males and females versus type Is. In summary, rapid steroid action on VPG activity is uncoupled from gonadal phenotype (convergent between type II males and females), whereas the receptor-mediated mechanisms of androgen action are predicted by gonadal phenotype (both male morphs are sensitive to androgen receptor blockade, whereas females are not). A comparable mix of neuroendocrine traits may explain the widespread distribution of intrasexual behavioral phenotypes among teleosts and vertebrates in general. Moreover, the fundamental organization/activation principles that predict the steroid-dependent expression of "maleness" and "femaleness" may now include rapid steroid actions on the neurophysiological patterning of behavior.

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Neocortical Inhibitory Terminals Innervate Dendritic Spines Targeted by Thalamocortical Afferents

Yoshiyuki Kubota, Sayuri Hatada, Satoru Kondo, Fuyuki Karube, and Yasuo Kawaguchi

Division of Cerebral Circuitry, National Institute for Physiological Sciences, Okazaki, Aichi 444-8787, Japan

Fast inhibition in the cortex is gated primarily at GABAergic synapses formed by local interneurons onto postsynaptic targets. Although GABAergic inputs to the somata and axon initial segments of neocortical pyramidal neurons are associated with direct inhibition of action potential generation, the role of GABAergic inputs to distal dendritic segments, including spines, is less well characterized. Because a significant proportion of inhibitory input occurs on distal dendrites and spines, it will be important to determine whether these GABAergic synapses are formed selectively by certain classes of presynaptic cells onto specific postsynaptic elements. By electron microscopic observations of synapses formed by different subtypes of nonpyramidal cells, we found that a surprisingly large fraction (33.4 $\pm$ 9.3%) of terminals formed symmetrical synaptic junctions onto a subset of cortical spines that were mostly coinnervated by an asymmetrical terminal. Using VGLUT1 and VGLUT2 isoform of the glutamate vesicular transporter immunohistochemistry, we found that the double-innervated spines selectively received thalamocortical afferents expressing the VGLUT2 but almost never intracortical inputs expressing the VGLUT1. When comparing the volumes of differentially innervated spines and their synaptic junction areas, we found that spines innervated by VGLUT2-positive terminal were significantly larger than spines innervated by VGLUT1-positive terminal and that these spines had larger, and more often perforated, synapses than those of spines innervated by VGLUT1-positive afferent. These results demonstrate that inhibitory inputs to pyramidal cell spines may preferentially reduce thalamocortical rather than intracortical synaptic transmission and are therefore positioned to selectively gate extracortical information.

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Shaping of Motor Responses by Incentive Values through the Basal Ganglia

Benjamin Pasquereau,[1,4] Agnes Nadjar,[1,4] David Arkadir,[1,3,4] Erwan Bezard,[1] Michel Goillandeau,[1] Bernard Bioulac,[1,2,4] Christian Eric Gross,[1,2,4] and Thomas Boraud[1,4]

[1]Basal Gang, Laboratoire de Neurophysiologie, Centre National de la Recherche Scientifique, Unité Mixte de Recherche 5227, Université Victor Segalen, 33076 Bordeaux, France, [2]Centre Hospitalier Universitaire de Bordeaux, 33800 Bordeaux, France, [3]Interdisciplinary Center for Neural Computation, The Hebrew University, Jerusalem 91905, Israel, and [4]Laboratoire Franco-Israelien de Neurophysiologie et Neurophysique des Systemes, 33076 Bordeaux, France

The striatum is a key neural interface for cognitive and motor information processing in which associations between reward value and visual stimulus can be used to modify motor commands. It can guide action–selection processes that occur farther downstream in the basal ganglia (BG) circuit, by encoding the reward value of an action. Here, we report on the study of simultaneously recorded neurons in the dorsal striatum (input stage of the BG) and the internal pallidum (output stage of the BG) in two monkeys performing a center-out motor task in which the visual targets were associated with different reward probabilities. We show that the tuning curves of motor-related neurons in both structures are modulated by the value of the action before movement initiation and during its execution. The representations of values associated with different actions change dynamically during the task in the internal globus pallidus, with a significant increase in the number of encoding neurons for the chosen target at the onset of movement. This report sheds additional light on the functional differences between the input and output structures of the BG and supports the assertion that the dorsal basal ganglia are involved in movement-related decision-making processes based on incentive values.

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Anatomical Traces of Vocabulary Acquisition in the Adolescent Brain

HweeLing Lee,[1] Joseph T. Devlin,[2] Clare Shakeshaft,[1] Lauren H. Stewart,[3] Amanda Brennan,[1] Jen Glensman,[1] Katherine Pitcher,[5] Jenny Crinion,[1] Andrea Mechelli,[6] Richard S. J. Frackowiak,[1,7,8] David W. Green,[4] and Cathy J. Price[1]

[1]Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College London (UCL), London WC1N 3BG, United Kingdom, [2]Department of Clinical Neurology, University of Oxford, Oxford OX2 6HE, United Kingdom, [3]Subdepartment of Clinical Health Psychology and [4]Department of Psychology, UCL, London WC1E 6BT, United Kingdom, [5]School of Psychology, University of Kwa-Zulu Natal, 4041 Durban, South Africa, [6]Institute of Psychiatry, King's College, London SE5 8AF, United Kingdom, [7]Département d'Études Cognitives, École Normale Superieure, 75230 Paris, France, and [8]Istituti di Ricovero e Cura a Carattere Scientifico Santa Lucia, 00179 Rome, Italy

A surprising discovery in recent years is that the structure of the adult human brain changes when a new cognitive or motor skill is learned. This effect is seen as a change in local gray or white matter density that correlates with behavioral measures. Critically, however, the cognitive and anatomical mechanisms underlying these learning-related structural brain changes remain unknown. Here, we combined brain imaging, detailed behavioral analyses, and white matter tractography in English-speaking monolingual adolescents to show that a critical linguistic prerequisite (namely, knowledge of vocabulary) is proportionately related to relative gray matter density in bilateral posterior supramarginal gyri. The effect was specific to the number of words learned, regardless of verbal fluency or other cognitive abilities. The identified region was found to have direct connections to other inferior parietal areas that separately process either the sounds of words or their meanings, suggesting that the posterior supramarginal gyrus plays a role in linking the basic components of vocabulary knowledge. Together, these analyses highlight the cognitive and anatomical mechanisms that mediate an essential language skill.

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NEUROBIOLOGY OF DISEASE

A *Drosophila* Model of Mutant Human Parkin-Induced Toxicity Demonstrates Selective Loss of Dopaminergic Neurons and Dependence on Cellular Dopamine

Tzu-Kang Sang,[1,2]* Hui-Yun Chang,[3]* George M. Lawless,[1] Anuradha Ratnaparkhi,[1] Lisa Mee,[1] Larry C. Ackerson,[3] Nigel T. Maidment,[3,4,5,6] David E. Krantz,[3,4,5] and George R. Jackson[1,4,6]

[1]Neurogenetics and Movement Disorders Programs, Department of Neurology, and [2]Institute of Biotechnology and Department of Life Science, National Tsing Hua University, Taiwan, Republic of China, and [3]Department of Psychiatry and Biobehavioral Sciences, [4]Brain Research Institute, [5]Hatos Center for Neuropharmacology, and [6]Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, California 90095

Mutations in human parkin have been identified in familial Parkinson's disease and in some sporadic cases. Here, we report that expression of mutant but not wild-type human parkin in *Drosophila* causes age-dependent, selective degeneration of dopaminergic (DA) neurons accompanied by a progressive motor impairment. Overexpression or knockdown of the *Drosophila* vesicular monoamine transporter, which regulates cytosolic DA homeostasis, partially rescues or exacerbates, respectively, the degenerative phenotypes caused by mutant human parkin. These results support a model in which the vulnerability of DA neurons to parkin-induced neurotoxicity results from the interaction of mutant parkin with cytoplasmic dopamine.

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NKG2D-Mediated Cytotoxicity toward Oligodendrocytes Suggests a Mechanism for Tissue Injury in Multiple Sclerosis

Philippe Saikali,[1] Jack P. Antel,[1] Jia Newcombe,[3] Zhihong Chen,[4] Mark Freedman,[4] Manon Blain,[1] Romain Cayrol,[5] Alexandre Prat,[5] Jeffery A. Hall,[2] and Nathalie Arbour[1,5]

[1]Neuroimmunology Unit, Montreal Neurological Institute, and [2]Division of Neurosurgery, McGill University, Montreal, Quebec, Canada H3A 2B4, [3]NeuroResource, University College London, Institute of Neurology, London WC1N 1PJ, United Kingdom, [4]Ottawa Hospital, University of Ottawa, Ottawa, Ontario, Canada K1H 8L6, and [5]Research Center-Centre Hospitalier de l'Université de Montréal, University of Montreal, Montreal, Quebec, Canada H2L 4M1

NKG2D is an activating or coactivating receptor expressed on human natural killer (NK) cells, CD8$^+$ T cells, and γ/δ T cells. NKG2D ligands have been detected on many tumor cell types and can be induced on nontransformed cells by environmental signals including DNA damage and inflammation. We investigated the contribution of NKG2D–NKG2D ligand interaction on CNS-directed immune responses. We observed that primary cultures of human adult oligodendrocytes and fetal astrocytes expressed ligands for NKG2D *in vitro* whereas neurons, microglia, and adult astrocytes did not. Disruption of the NKG2D–NKG2D ligand interaction using blocking antibodies significantly inhibited killing of primary human oligodendrocytes mediated by activated human NK cells, γ/δ T cells, and allo-reactive CD8$^+$ T cells. NKG2D ligands [major histocompatibility complex class I chain-related molecules A and B (MICA/B)] were detected in groups of cells and colocalized with an oligodendrocyte marker (adenomatous polyposis coli) in white matter sections obtained from multiple sclerosis lesions but not in normal control samples. CD8$^+$ T cells could be detected in close proximity to MICA/B+ cells within multiple sclerosis lesions, supporting an *in vivo* interaction between these immune effectors and stressed MICA/B-expressing oligodendrocytes. These results imply that NKG2D–NKG2D ligand interaction can potentially contribute to cytotoxic responses mediated by activated immune effector cells in the inflamed CNS, as observed in multiple sclerosis.

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