

This Week in The Journal

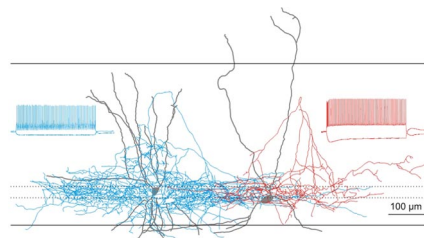
● Cellular/Molecular

Actions of Cannabinoids and Opioids in Inhibitory Networks

Lindsey L. Glickfeld, Bassam V. Atallah, and Massimo Scanziani

(see pages 1824–1832)

Hippocampal pyramidal neurons receive somatic inhibitory inputs from two types of basket cells—regular spiking (RS) and fast spiking (FS) cells—that are active at different times. Both cannabinoids and opioids act presynaptically to reduce this inhibition, but as shown by electrophysiological experiments in rat slice cultures by Glickfeld et al., the actions of cannabinoids and opioids are largely restricted to different classes of basket cells. Cannabinoid receptor (CB1R) agonists acted solely on RS cells, reducing their inhibition of pyramidal cells and of other RS cells. In contrast, μ -opioid receptor (μ OR) agonists primarily reduced pyramidal cell inhibition by FS cells, but they also reduced inhibition mediated by some RS cells, suggesting that the segregation of the two receptor types is not complete. Both agonists reduced polysynaptic inhibition of pyramidal cells evoked by stimulation of Schaffer collaterals, but the timing of the effects suggested that CB1Rs reduced feedback inhibition, whereas μ ORs reduced feedforward inhibition.



Reconstructions of an FS (left; blue, axon; gray, dendrite) and an RS (right; red, axon; gray, dendrite) basket cell. Insets, Voltage traces from the cells shown in response to depolarizing and hyperpolarizing steps. See the article by Glickfeld et al. for details.

▲ Development/Plasticity/Repair

Effects of Prenatal Alcohol Exposure on GABAergic Neurons

Virginia C. Cuzon, Pamela W. L. Yeh, Yuchio Yanagawa, Kunihiko Obata, and Hermes H. Yeh

(see pages 1854–1864)

The adverse effects of excessive alcohol consumption during pregnancy are clearly seen in fetal alcohol syndrome, but even small doses can be damaging. This week, Cuzon et al. report that chronic exposure to low levels of ethanol (producing a blood alcohol content three times lower than that defining legal intoxication in the United States) resulted in accelerated migration and differentiation of cortical GABAergic interneurons in embryonic rats. Whole-cell electrophysiological recordings in cortical slices detected elevated GABA levels and increased sensitivity of GABAergic neurons to GABA in ethanol-exposed embryos. Blocking GABA receptors prevented ethanol-induced acceleration of migration, whereas bath application of GABA increased migration in control slices, suggesting that the effects of ethanol are mediated through GABA signaling. Although more GABAergic interneurons were present in the cortex at embryonic day 14 in ethanol-exposed rats, previous studies suggest that many of these neurons must die, because adult brains of ethanol-exposed embryos have fewer GABAergic neurons than controls.

■ Behavioral/Systems/Cognitive

Sensory Processing in the Trigeminal Nucleus

Takahiro Furuta, Elena Timofeeva, Kouichi Nakamura, Keiko Okamoto-Furuta, Masaya Togo, Takeshi Kaneko, and Martin Deschênes

(see pages 1789–1797)

The vibrissal system of rodents, which is used to navigate and to recognize objects, has been intensively studied in the somatosensory barrel cortex and the thalamus. In contrast, little is known about neural interactions in the first sensory-processing stage,

the trigeminal nuclei. Neurons in the principal trigeminal nucleus (PrV) respond to movement of single or multiple whiskers and are inhibited by movements of adjacent whiskers. Although receptive field size and surround inhibition have been thought to arise from connections between trigeminal subnuclei, evidence for this has remained elusive. Now Furuta et al. have used lesions, electrophysiological recordings, tract tracing, *in situ* hybridization, and electron microscopy to show definitively that PrV receives GABAergic projections from the interpolaris subnucleus and glutamatergic inputs from the caudalis subnucleus. Ablating inputs from interpolaris eliminated surround inhibition of PrV neurons, providing strong evidence that intersubnuclear connections shape the ascending output of trigeminal nuclei.

◆ Neurobiology of Disease

Eliminating Brain Tumors with Viruses

Koray Özdoğan, Guido Wollmann, Joseph M. Piepmeyer, and Anthony N. van den Pol

(see pages 1882–1893)

Viral targeting may become the first effective treatment for glioblastoma, if the approach presented by Özdoğan et al. continues to hold promise. Previous attempts that used nonreplicating viruses to attack gliomas failed because the infected area remained small. These authors therefore used a replicating vesicular stomatitis virus to target expansive tumor implants in mice. A single intravenous injection of virus successfully and simultaneously infected multiple tumors within and outside the brain. Several different types of tumors were infected, whereas normal cells were almost completely spared. By fluorescently labeling both tumor and viruses, the authors could observe the progress of infection through a cranial window. Initial infection occurred focally, but as the virus replicated, infected cells died and the infection quickly spread to encompass the entire tumor. Infection of some migrating tumor cells suggested that viral treatment may prove effective against infiltrating tumors as well.

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Cover legend: Immunofluorescence staining for otoferlin expression in whole mounts of mouse organ of Corti and crista ampullaris. Both cochlear and vestibular sensory hair cells exhibit an intense otoferlin staining. A defect in otoferlin expression silences the auditory hair cell ribbon synapse. For more information, see the article by Beurg et al. in this issue (pages 1798–1803).

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Calcium- and Otoferlin-Dependent Exocytosis by Immature Outer Hair Cells

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Immature cochlear outer hair cells (OHCs) make transient synaptic contacts (ribbon synapses) with type I afferent nerve fibers, but direct evidence of synaptic vesicle exocytosis is still missing. We thus investigated calcium-dependent exocytosis in murine OHCs at postnatal day 2 (P2)–P3, a developmental stage when calcium current maximum amplitude was the highest. By using time-resolved patch-clamp capacitance measurements, we show that voltage step activation of L-type calcium channels triggers fast membrane capacitance increase. Capacitance increase displayed two kinetic components, which are likely to reflect two functionally distinct pools of synaptic vesicles, a readily releasable pool (RRP; $\tau = 79$ ms) and a slowly releasable pool ($\tau = 870$ ms). The RRP size and maximal release rate were estimated at ~ 1200 vesicles and $\sim 15,000$ vesicles/s, respectively. In addition, we found a linear relationship between capacitance increase and calcium influx, like in mature inner hair cells (IHCs). These results give strong support to the existence of efficient calcium-dependent neurotransmitter release in immature OHCs. Moreover, we show that immature OHCs, just like immature IHCs, are able to produce regenerative calcium-dependent action potentials that could trigger synaptic exocytosis *in vivo*. Finally, the evoked membrane capacitance increases were abolished in P2–P3 OHCs from mutant *Otof*^{-/-} mice defective for otoferlin, despite normal calcium currents. We conclude that otoferlin, the putative major calcium sensor at IHC ribbon synapses, is essential to synaptic exocytosis in immature OHCs too.

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Microstructural Correlates of Infant Functional Development: Example of the Visual Pathways

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The development of cognitive functions during childhood relies on several neuroanatomical maturation processes. Among these processes is myelination of the white matter pathways, which speeds up electrical conduction. Quantitative indices of such structural processes can be obtained *in vivo* with diffusion tensor imaging (DTI), but their physiological significance remains uncertain. Here, we investigated the microstructural correlates of early functional development by combining DTI and visual event-related potentials (VEPs) in 15 one- to 4-month-old healthy infants. Interindividual variations of the apparent conduction speed, computed from the latency of the first positive VEP wave (P1), were significantly correlated with the infants' age and DTI indices measured in the optic radiations. This demonstrates that fractional anisotropy and transverse diffusivity are structural markers of functionally efficient myelination. Moreover, these indices computed along the optic radiations showed an early wave of maturation in the anterior region, with the posterior region catching up later in development, which suggests two asynchronous fronts of myelination in both the geniculocortical and corticogeniculate fibers. Thus, in addition to microstructural information, DTI provides noninvasive exquisite information on the functional development of the brain in human infants.

The Journal of Neuroscience, February 20, 2008 • 28(8):1943–1948

cAMP Response Element-Binding Protein 1 Feedback Loop Is Necessary for Consolidation of Long-Term Synaptic Facilitation in *Aplysia*

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The transcription factor cAMP response element (CRE)-binding protein (CREB) plays an essential role in the induction of many forms of long-term synaptic plasticity. Levels of CREB1, the *Aplysia* homolog of CREB, show sustained elevations for several hours after the induction of long-term synaptic facilitation (LTF). Furthermore, CREB1 binds to the promoter of its own gene. These results suggest the existence of a CREB1-positive feedback loop that contributes to the consolidation of LTF. In the present study, we provide a detailed, quantitative characterization of the dynamics of CREB1 mRNA and protein as well as CREB1 phosphorylation after LTF induction. Injections of CRE oligonucleotides prevented the increase in CREB1 in response to 5-HT, corroborating the existence of the CREB1 feedback loop. This loop probably sustains CRE-dependent gene transcription, which remains elevated for at least 12 h after LTF induction. LTF is blocked by injection of CREB1 antibody after the induction phase, suggesting that the CREB1-positive feedback is required for consolidation of LTF.

The Journal of Neuroscience, February 20, 2008 • 28(8):1970–1976

The Good, the Bad, and the Cell Type-Specific Roles of Hypoxia Inducible Factor-1 α in Neurons and Astrocytes

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Hypoxia inducible factor-1 α (HIF-1 α) is a key regulator of oxygen homeostasis, because it is responsible for the regulation of genes involved in glycolysis, erythropoiesis, angiogenesis, and apoptosis. In the CNS, HIF-1 α is stabilized by insults associated with hypoxia and ischemia. Because its many target genes mediate both adaptive and pathological processes, the role of HIF-1 α in neuronal survival is debated. Although neuronal HIF-1 α function has been the topic of several studies, the role of HIF-1 α function in astrocytes has received much less attention. To characterize the role of HIF-1 α in neurons and astrocytes, we induced loss of HIF-1 α function specifically in neurons, astrocytes, or both cell types in neuron/astrocyte cocultures exposed to hypoxia. Although loss of HIF-1 α function in neurons reduced neuronal viability during hypoxia, selective loss of HIF-1 function in astrocytes markedly protected neurons from hypoxic-induced neuronal death. Although the pathological processes induced by HIF-1 α in astrocytes remain to be defined, induction of inducible nitric oxide synthase likely contributes to the pathological process. This study delineates, for the first time, a cell type-specific action for HIF-1 α within astrocytes and neurons.

The Journal of Neuroscience, February 20, 2008 • 28(8):1988–1993

Articles

CELLULAR/MOLECULAR

Noradrenergic Modulation of Electrical Coupling in GABAergic Networks of the Hippocampus

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Noradrenergic modulation of cortical circuits is involved in information processing, regulation of higher functions, and prevention of epileptic activity. Here, we studied the effects of noradrenaline on the functional connectivity of GABAergic networks of the hippocampus and show that electrical synapses between interneurons are a novel target of noradrenergic modulation *in vitro*. Application of noradrenaline or of the selective β -adrenergic agonist isoproterenol decreased gap junction-based coupling in paired recordings from stratum lacunosum-moleculare interneurons by \sim 40%. Similar results were obtained after pharmacological stimulation of the adenylyl cyclase with forskolin. In contrast, the adenylyl cyclase antagonist MDL12330A [*cis*-*N*-(2-phenylcyclopentyl)azacyclotridec-1-en-2-amine] or the specific protein kinase A (PKA) inhibitor H89 [*N*-[2-(*p*-bromocinnamyl-amino)ethyl]-5-isoquinolinesulfonamide dihydrochloride] enhanced the basal strength of coupling by \sim 30%. In addition, PKA-mediated phosphorylation was critical for both isoproterenol- and forskolin-dependent regulation of coupling, because inclusion of the PKA antagonist KT5720 [(9*S*,10*R*,12*R*)-2,3,9,10,11,12-hexahydro-10-hydroxy-9-methyl-1-oxo-9,12-epoxy-1*H*-diindolo[1,2,3-*fg*:3',2',1'-*kl*]pyrrolo[3,4-*i*][1,6]benzodiazocine-10-carboxylic acid hexyl ester] in the recording pipettes prevented modulation.

Lastly, we studied the effects of β -adrenergic modulation on mixed polysynaptic transmission within the GABAergic network. Isoproterenol depressed propagation of GABA_A receptor-mediated synaptic currents, but did not change significantly direct GABAergic input, indicating that regulation of electrical coupling adds flexibility to the information flow generated by chemical synapses.

In conclusion, activation of β -adrenergic receptors in stratum lacunosum-moleculare GABAergic networks reduces electrical synaptic transmission via a cAMP/PKA signaling cascade, and affects the degree of synaptic divergence within the circuit. We propose that this dynamic modulation and interplay between electrical and chemical synaptic transmission in GABAergic networks contributes to the tuning of memory processes *in vivo*, and prevents hypersynchronous activity.

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Complementary Modulation of Somatic Inhibition by Opioids and Cannabinoids

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Somatic inhibition, which is critical for determining the spike output of principal cells, is mediated by two physiologically distinct classes of GABAergic interneurons called basket cells. In the hippocampus, despite both targeting the somatic membrane of CA1 pyramidal cells, these two classes of basket cells are active at different times. Differential modulation of these two types of basket cells could hence be important for regulating the activity patterns of CA1 pyramidal cells at very specific periods during ongoing activity. Indeed, cannabinoids selectively suppress the output of one class of basket cell. Whether opioids, another major modulator of inhibition in the hippocampus, also selectively suppress somatic inhibition is not known. Here, we show that basket cells are selectively modulated by either opioids or cannabinoids, but not both. We also find that basket cells are integrated into specific inhibitory subnetworks that are themselves under differential control of opioids and cannabinoids. Furthermore, because the two interneuron types are activated at different times, opioids and cannabinoids suppress different epochs of inhibition. This cell-type specific sensitivity to neuromodulators allows for a fine control of the temporal structure of hippocampal activity.

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Ca²⁺/CaM Controls Ca²⁺-Dependent Inactivation of NMDA Receptors by Dimerizing the NR1 C Termini

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Ca²⁺ influx through NMDA receptors (NMDARs) leads to channel inactivation, which limits Ca²⁺ entry and protects against excitotoxicity. Extensive functional data suggests that this Ca²⁺-dependent inactivation (CDI) requires both calmodulin (CaM) binding to the C0 cassette of the NR1 subunit's C terminus (CT) and regulation by α -actinin-2, but a molecular understanding of CDI has been elusive. Here we used a number of methods to analyze the molecular nature of the interaction among CaM, α -actinin-2, and the NR1 CT. We found that a single CaM binds to two NR1 CTs in a Ca²⁺-dependent manner and promotes their reversible "dimerization." Expressed NMDARs containing NR1 concatamers in which the NR1 C termini are "uncoupled" display markedly reduced CDI. In contrast to current models, α -actinin-2 does not bind to the NR1 CT. We propose a new model for CDI in which the noncanonical Ca²⁺/CaM-dependent dimerization of the two NR1 subunits inactivates the channel by propagating a conformational change from the short NR1 CT to the nearby channel pore.

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Release of the Styryl Dyes from Single Synaptic Vesicles in Hippocampal Neurons

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In small presynaptic boutons in brain, synaptic vesicles are thought not to merge with the plasma membrane when they release transmitter, but instead to close their fusion pores and survive intact for future use (kiss-and-run exocytosis). The strongest evidence for this idea is the slow and incomplete release of the fluorescent membrane marker, FM1-43 [*N*-(3-triethylammoniumpropyl)-4-(4-(dibutylamino)styryl) pyridinium dibromide], from single vesicles. We investigated the release of FM1-43 from sparse cultures of hippocampal neurons grown on coverslips with no glia. This allowed presynaptic boutons to be imaged at favorable signal-to-noise ratio. Sparingly stained boutons were imaged at high time resolution, while high-frequency electrical stimulation caused exocytosis. The release of FM1-43 was quantal and occurred in abrupt steps, each representing a single fusion event. The fluorescence of vesicle clusters traveling along axons had a distribution with the same quantal size, indicating that a vesicle releases all the dye it contains. In most fusion events, the time constant of dye release was <100 ms, and slower release was rarely observed. After exocytosis, no FM1-43 could be detected in the axon to either side of a bouton, indicating that dye was released before it could spread. Our results are consistent with synaptic vesicles fusing fully with the plasma membrane during high-frequency stimulation.

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Vesicle Priming and Recruitment by ubMunc13-2 Are Differentially Regulated by Calcium and Calmodulin

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Ca²⁺ regulates multiple processes in nerve terminals, including synaptic vesicle recruitment, priming, and fusion. Munc13s, the mammalian homologs of *Caenorhabditis elegans* Unc13, are essential vesicle-priming proteins and contain multiple regulatory domains that bind second messengers such as diacylglycerol and Ca²⁺/calmodulin (Ca²⁺/CaM). Binding of Ca²⁺/CaM is necessary for the regulatory effect that allows Munc13-1 and ubMunc13-2 to promote short-term synaptic plasticity. However, the relative contributions of Ca²⁺ and Ca²⁺/CaM to vesicle priming and recruitment by Munc13 are not known. Here, we investigated the effect of Ca²⁺/CaM binding on ubMunc13-2 activity in chromaffin cells via membrane-capacitance measurements and a detailed simulation of the exocytotic machinery. Stimulating secretion under various basal Ca²⁺ concentrations from cells overexpressing either ubMunc13-2 or a ubMunc13-2 mutant deficient in CaM binding enabled a distinction between the effects of Ca²⁺ and Ca²⁺/CaM. We show that vesicle priming by ubMunc13-2 is Ca²⁺ dependent but independent of CaM binding to ubMunc13-2. However, Ca²⁺/CaM binding to ubMunc13-2 specifically promotes vesicle recruitment during ongoing stimulation. Based on the experimental data and our simulation, we propose that ubMunc13-2 is activated by two Ca²⁺-dependent processes: a slow activation mode operating at low Ca²⁺ concentrations, in which ubMunc13-2 acts as a priming switch, and a fast mode at high Ca²⁺ concentrations, in which ubMunc13-2 is activated in a Ca²⁺/CaM-dependent manner and accelerates vesicle recruitment and maturation during stimulation. These different Ca²⁺ activation steps determine the kinetic properties of exocytosis and vesicle recruitment and can thus alter plasticity and efficacy of transmitter release.

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Ethanol Consumption during Early Pregnancy Alters the Disposition of Tangentially Migrating GABAergic Interneurons in the Fetal Cortex

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Consumption of alcohol (ethanol) during pregnancy can lead to developmental defects in the offspring, the most devastating being the constellation of symptoms collectively referred to as fetal alcohol syndrome (FAS). In the brain, a hallmark of FAS is abnormal cerebral cortical morphology consistent with insult during corticogenesis. Here, we report that exposure to a relatively low level of ethanol *in utero* (average maternal and fetal blood alcohol level of 25 mg/dl) promotes premature tangential migration into the cortical anlage of primordial GABAergic interneurons, including those originating in the medial ganglionic eminence (MGE). This ethanol-induced effect was evident *in vivo* at embryonic day 14.5 (E14.5) in *GAD67* knock-in and *BAC-Lhx6* embryos, as well as *in vitro* in isotypic telencephalic slice cocultures obtained from E14.5 embryos exposed to ethanol *in utero*. Analysis of heterotypic cocultures indicated that both cell-intrinsic and -extrinsic factors contribute to the aberrant migratory profile of MGE-derived cells. In this light, we provide evidence for an interaction between ethanol exposure *in utero* and the embryonic GABAergic system. Exposure to ethanol *in utero* elevated the ambient level of GABA and increased the sensitivity to GABA of MGE-derived cells. Our results uncovered for the first time an effect of ethanol consumption during pregnancy on the embryonic development of GABAergic cortical interneurons. We propose that ethanol exerts its effect on the tangential migration of GABAergic interneurons extrinsically by modulating extracellular levels of GABA and intrinsically by altering GABA_A receptor function.

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TGF β -Smad2 Signaling Regulates the Cdh1-APC/SnoN Pathway of Axonal Morphogenesis

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Axon growth is critical to the establishment of neuronal connectivity. The E3 ubiquitin ligase Cdh1-anaphase-promoting complex (Cdh1-APC) and its substrate the transcriptional modulator SnoN form a cell-intrinsic pathway that orchestrates axonal morphogenesis in the mammalian brain. How the Cdh1-APC/SnoN pathway is controlled in the nervous system remained unknown. Here, we report that the TGF β -regulated signaling protein Smad2 plays a key role in regulating the Cdh1-APC/SnoN pathway in neurons. We find that Smad2 is expressed in primary granule neurons of the developing rat cerebellar cortex. The Smad signaling pathway is basally activated in neurons. Endogenous Smad2 is phosphorylated, localized in the nucleus, and forms a physical complex with endogenous SnoN in granule neurons. Inhibition of Smad signaling by several distinct approaches, including genetic knock-down of Smad2, stimulates axonal growth. Biochemical evidence and genetic epistasis analyses reveal that Smad2 acts upstream of SnoN in a shared pathway with Cdh1-APC in the control of axonal growth. Remarkably, Smad2 knock-down also overrides the ability of adult rat myelin to inhibit axonal growth. Collectively, our findings define a novel function for Smad2 in regulation of the Cdh1-APC/SnoN cell-intrinsic pathway of axonal morphogenesis, and suggest that inhibition of Smad signaling may hold therapeutic potential in stimulating axonal growth after injury in the CNS.

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Inhibitory Gating of Vibrissal Inputs in the Brainstem

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Trigeminal sensory nuclei are the first processing stage in the vibrissal system of rodents. They feature separate populations of thalamic projecting cells and a rich network of intersubnuclear connections, so that what is conveyed to the cortex by each of the ascending pathways of vibrissal information depends on local transactions that occur in the brainstem. In the present study, we examined the nature of these intersubnuclear connections by combining electrolytic lesions with electrophysiological recordings, retrograde labeling with *in situ* hybridization, and anterograde labeling with immunoelectron microscopy. Together, these different approaches provide conclusive evidence that the principal trigeminal nucleus receives inhibitory GABAergic projections from the caudal sector of the interpolaris subnucleus, and excitatory glutamatergic projections from the caudalis subnucleus. These results raise the possibility that, by controlling the activity of intersubnuclear projecting cells, brain regions that project to the spinal trigeminal nuclei may take an active part in selecting the type of vibrissal information that is conveyed through the lemniscal pathway.

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Prestimulus Oscillatory Activity in the Alpha Band Predicts Visual Discrimination Ability

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Although the resting and baseline states of the human electroencephalogram and magnetoencephalogram (MEG) are dominated by oscillations in the alpha band (~10 Hz), the functional role of these oscillations remains unclear. In this study we used MEG to investigate how spontaneous oscillations in humans presented before visual stimuli modulate visual perception. Subjects had to report if there was a subtle difference in gray levels between two superimposed presented discs. We then compared the prestimulus brain activity for correctly (hits) versus incorrectly (misses) identified stimuli. We found that visual discrimination ability decreased with an increase in prestimulus alpha power. Given that reaction times did not vary systematically with prestimulus alpha power changes in vigilance are not likely to explain the change in discrimination ability. Source reconstruction using spatial filters allowed us to identify the brain areas accounting for this effect. The dominant sources modulating visual perception were localized around the parieto-occipital sulcus. We suggest that the parieto-occipital alpha power reflects functional inhibition imposed by higher level areas, which serves to modulate the gain of the visual stream.

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Activation of the Medial Septum Reverses Age-Related Hippocampal Encoding Deficits: A Place Field Analysis

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When a rat runs through a familiar environment, the hippocampus retrieves a previously stored spatial representation of the environment. When the environment is modified a new representation is seen, presumably corresponding to the hippocampus encoding the new information. The medial septum is hypothesized to modulate whether the hippocampus engages in retrieval or encoding. The cholinergic agonist carbachol was infused into the medial septum, and hippocampal CA1 place cells were recorded in freely moving rats. In a familiar environment, septal activation impaired the retrieval of a previously stored hippocampal place cell representation regardless of age. When the environment was changed, medial septal activation impaired the encoding process in young, but facilitated the encoding of the new information in aged rats. Moreover, the improved encoding was evident during a subsequent exposure to the modified environment 24 h later. The findings support the role the septum plays in modulating hippocampal retrieval/encoding states. Furthermore, our data indicate a mechanism of age-related cognitive impairment.

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Recurrent Synaptic Input and the Timing of Gamma-Frequency-Modulated Firing of Pyramidal Cells during Neocortical “UP” States

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Gamma (γ) oscillation, a hallmark of cortical activity during sensory processing and cognition, occurs during persistent, self-sustained activity or “UP” states, which are thought to be maintained by recurrent synaptic inputs to pyramidal cells. During neocortical “UP” states, excitatory regular spiking (RS) (pyramidal) cells and inhibitory fast spiking (FS) (basket) cells fire with distinct phase distributions relative to the γ oscillation in the local field potential. Evidence suggests that γ -modulated RS \rightarrow FS input serves to synchronize the interneurons and hence to generate γ -modulated FS \rightarrow RS drive. How RS \rightarrow RS recurrent input shapes both self-sustained activity and γ -modulated phasic firing, although, is unclear. Here, we investigate this by reconstructing γ -modulated synaptic input to RS cells using the conductance injection (dynamic clamp) technique in cortical slices. We find that, to show lifelike γ -modulated firing, RS cells require strongly γ -modulated, low-latency inhibitory inputs from FS cells but little or no γ -modulation from recurrent RS \rightarrow RS connections. We suggest that this demodulation of recurrent excitation, compared with inhibition, reflects several possible effects, including distributed propagation delays and integration of excitation over wider areas of cortex, and maximizes the capacity for representing information by the timing of recurrent excitation.

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An Input-Representing Interneuron Regulates Spike Timing and Thereby Phase Switching in a Motor Network

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Despite the importance of spike-timing regulation in network functioning, little is known about this regulation at the cellular level. In the *Aplysia* feeding network, we show that interneuron B65 regulates the timing of the spike initiation of phase-switch neurons B64 and cerebral-buccal interneuron-5/6 (CBI-5/6), and thereby determines the identity of the neuron that acts as a protraction terminator. Previous work showed that B64 begins to fire before the end of protraction phase and terminates protraction in

CBI-2-elicited ingestive, but not in CBI-2-elicited egestive programs, thus indicating that the spike timing and phase-switching function of B64 depend on the type of the central pattern generator (CPG)-elicited response rather than on the input used to activate the CPG. Here, we find that CBI-5/6 is a protraction terminator in egestive programs elicited by the esophageal nerve (EN), but not by CBI-2, thus indicating that, in contrast to B64, the spike timing and protraction-terminating function of CBI-5/6 depends on the input to the CPG rather than the response type. Interestingly, B65 activity also depends on the input in that B65 is highly active in EN-elicited programs, but not in CBI-2-elicited programs independent of whether the programs are ingestive or egestive. Notably, during EN-elicited egestive programs, hyperpolarization of B65 delays the onset of CBI-5/6 firing, whereas in CBI-2-elicited ingestive programs, B65 stimulation simultaneously advances CBI-5/6 firing and delays B64 firing, thereby substituting CBI-5/6 for B64 as the protraction terminator. Thus, we identified a neural mechanism that, in an input-dependent manner, regulates spike timing and thereby the functional role of specific neurons.

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Nonlinearities and Contextual Influences in Auditory Cortical Responses Modeled with Multilinear Spectrotemporal Methods

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The relationship between a sound and its neural representation in the auditory cortex remains elusive. Simple measures such as the frequency response area or frequency tuning curve provide little insight into the function of the auditory cortex in complex sound environments. Spectrotemporal receptive field (STRF) models, despite their descriptive potential, perform poorly when used to predict auditory cortical responses, showing that nonlinear features of cortical response functions, which are not captured by STRFs, are functionally important. We introduce a new approach to the description of auditory cortical responses, using multilinear modeling methods. These descriptions simultaneously account for several nonlinearities in the stimulus–response functions of auditory cortical neurons, including adaptation, spectral interactions, and nonlinear sensitivity to sound level. The models reveal multiple inseparabilities in cortical processing of time lag, frequency, and sound level, and suggest functional mechanisms by which auditory cortical neurons are sensitive to stimulus context. By explicitly modeling these contextual influences, the models are able to predict auditory cortical responses more accurately than are STRF models. In addition, they can explain some forms of stimulus dependence in STRFs that were previously poorly understood.

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Activation of Muscarinic Receptors in Rat Bladder Sensory Pathways Alters Reflex Bladder Activity

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Antimuscarinic drugs affect bladder sensory symptoms such as urgency and frequency, presumably by acting on muscarinic acetylcholine receptors (mAChRs) located in bladder sensory pathways including primary afferent nerves and urothelium. However, the expression and the function of these receptors are not well understood. This study investigated the role of mAChRs in bladder sensory pathways *in vivo* in urethane anesthetized rats. Intravesical administration of the mAChR agonist oxotremorine methiodide (OxoM) elicited concentration-dependent excitatory and inhibitory effects on the frequency of voiding. These effects were blocked by intravesical administration of the mAChR antagonist atropine methyl nitrate (5 μ M) and were absent in rats pretreated with capsaicin to desensitize C-fiber afferent nerves. Low concentrations of OxoM (5 μ M) decreased voiding frequency by \sim 30%, an effect blunted by inhibiting nitric oxide (NO) synthesis with L-NAME (*N*_ω-nitro-L-arginine methyl ester hydrochloride; 5 mg/kg; i.v.). High concentrations of OxoM (40 μ M) increased voiding frequency by \sim 45%, an effect blunted by blocking purinergic receptors with PPADS (0.1–1 mM; intravesically). mAChR agonists stimulated release of ATP from cultured urothelial cells. Intravenous administration of OxoM (0.01–5 μ g/kg) did not mimic the intravesical effects on voiding frequency. These results suggest that activation of mAChRs located near the luminal surface of the bladder affects voiding functions via mechanisms involving ATP and NO release presumably from the urothelium, that in turn could act on bladder C-fiber afferent nerves to alter their firing properties. These findings suggest that the urothelial-afferent nerve interactions can influence reflex voiding function.

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NEUROBIOLOGY OF DISEASE

An Aggregate-Inducing Peripherin Isoform Generated through Intron Retention Is Upregulated in Amyotrophic Lateral Sclerosis and Associated with Disease Pathology

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The neuronal intermediate filament protein peripherin is a component of ubiquitinated inclusions and of axonal spheroids in amyotrophic lateral sclerosis (ALS). Overexpression of peripherin causes motor neuron degeneration in transgenic mice and variations within the peripherin gene have been identified in ALS cases. We have

shown previously the abnormal expression of a neurotoxic peripherin splice variant in transgenic mice expressing mutant superoxide dismutase-1. These findings indicated that abnormalities of peripherin splicing may occur in ALS. In the current study, peripherin splice variants were identified by reverse transcription-PCR of human neuronal RNA and comparisons in expression made between control and ALS spinal cord using Western blot analysis and immunocytochemistry. Using this approach we have identified a novel peripherin transcript retaining introns 3 and 4 that results in a 28 kDa splice isoform, designated Per 28. Using an antibody specific to Per 28, we show that this isoform is expressed at low stoichiometric levels from the peripherin gene, however causes peripherin aggregation when its expression is upregulated. Importantly we show an upregulation of Per 28 expression in ALS compared with controls, at both the mRNA and protein levels, and that Per 28 is associated with disease pathology, specifically round inclusions. These findings are the first to establish that peripherin splicing abnormalities occur in ALS, generating aggregation-prone splice isoforms. *The Journal of Neuroscience*, February 20, 2008 • 28(8):1833–1840

Systemic Vesicular Stomatitis Virus Selectively Destroys Multifocal Glioma and Metastatic Carcinoma in Brain

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Metastatic tumors and malignant gliomas make up the majority of cancers in the brain. They are invariably fatal and there is currently no cure. From *in vitro* comparisons of a number of viruses, we selected one that appeared the best in selectively killing glioblastoma cells. This replication-competent virus, the glioma-adapted vesicular stomatitis virus strain VSVrp30a, was used for *in vivo* tests with the underlying view that infection of tumor cells will lead to an increase in the number of viruses subsequently released to kill additional tumor cells. Intravenous injection of VSVrp30a expressing a green fluorescent protein reporter, rapidly targeted and destroyed multiple types of human and mouse tumors implanted in the mouse brain, including glioblastoma and mammary tumors. When tumors were implanted both in the brain and peripherally, emulating systemic cancer metastasis, tumors inside and outside the brain were simultaneously infected. Intranasal inoculation, leading to olfactory nerve transport of the virus into the brain, selectively infected and killed olfactory bulb tumors. Neither control cortical wounds nor transplanted normal mouse or human cells were targeted, indicating viral tumor selectivity. Control viruses, including pseudorabies, adeno-associated, or replication-deficient VSV, did not infect the brain tumor. Confocal laser time-lapse imaging through a cranial window showed that intravenous VSV infects the tumor at multiple sites and kills migrating tumor cells. Disrupted tumor vasculature, suggested by dye leakage, may be the port of entry for intravenously delivered VSV. Quantitative PCR analysis of how VSVrp30a selectively infected tumor cells suggested multiple mechanisms, including cell surface binding and internalization.

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Locomotor Deficiencies and Aberrant Development of Subtype-Specific GABAergic Interneurons Caused by an Unliganded Thyroid Hormone Receptor $\alpha 1$

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Thyroid hormone (TH) deficiency during development causes severe and permanent neuronal damage, but the primary insult at the tissue level has remained unsolved. We have defined locomotor deficiencies in mice caused by a mutant thyroid hormone receptor $\alpha 1$ (TR $\alpha 1$) with potent aporeceptor activity attributable to reduced affinity to TH. This allowed identification of distinct functions that required either maternal supply of TH during early embryonic development or sufficient innate levels of hormone during late fetal development. In both instances, continued exposure to high levels of TH after birth and throughout life was needed. The hormonal dependencies correlated with severely delayed appearance of parvalbumin-immunoreactive GABAergic interneurons and increased numbers of calretinin-immunoreactive cells in the neocortex. This resulted in reduced numbers of fast spiking interneurons and defects in cortical network activity. The identification of locomotor deficiencies caused by insufficient supply of TH during fetal/perinatal development and their correlation with subtype-specific interneurons suggest a previously unknown basis for the neuronal consequences of endemic cretinism and untreated congenital hypothyroidism, and specifies TR $\alpha 1$ as the receptor isoform mediating these effects.

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