

This Week in The Journal

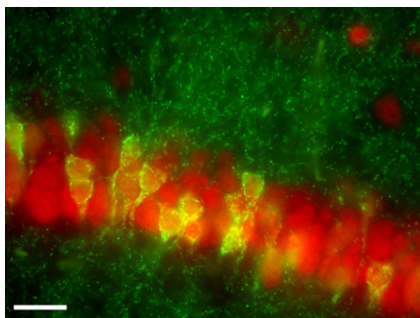
● Cellular/Molecular

Glowing Reports from Mitochondria

Krish Chandrasekaran, Julie L. Hazelton, Yu Wang, Gary Fiskum, and Tibor Kristian

(see pages 13123–13127)

In the fictional Star Wars universe, the Jedi have in their cells microscopic organisms, called midichlorians, which enable them to communicate with “the Force.” Us humans are stuck with just plain mitochondria. Although not as flashy, these ancient organelles perform essential metabolic functions. This week, Chandrasekaran et al. designed a system to explore their role in forebrain neurons. To specifically label neuronal mitochondria, the authors crossed mice expressing a mitochondrial-targeted, enhanced yellow fluorescent protein (eYFP) under control of a tetracycline-responsive element, with mice expressing the tetracycline-controlled transactivator protein driven by a forebrain (neuron)-specific promoter. In these mice, eYFP turned on in neuronal mitochondria when the animals received a doxycycline-free diet. With this model system, the authors will be able to ask all kinds of interesting questions, and in the best spirit of *The Journal of Neuroscience*, these mice will be made available to the community. May the force be with them!



Mitochondrial-targeted eYFP (green) is shown in CA1 pyramidal cells whose cell bodies were labeled with anti-NeuN antibodies (red). See the article by Chandrasekaran et al. for details.

▲ Development/Plasticity/Repair

The Repertoire of RNAs in Nerve Cell Processes

Michael M. Poon, Sang-Hyun Choi, Christina A. M. Jamieson, Daniel H. Geschwind, and Kelsey C. Martin

(see pages 13390–13399)

Neurons transcribe mRNAs in their cell bodies; a small fraction of these mRNAs then travel into dendrites where they are translated. This local translation provides a means for neurons to quickly alter the protein composition of synapses in response to a specific stimulus. To identify mRNAs localized to the dendrites of hippocampal neurons, Poon et al. grew the neurons on custom filters with etched 3 μm pores and then mechanically separated axons, dendrites, and glial processes from cell bodies. They identified >100 mRNAs potentially localized to these processes by microarray analysis. Nineteen mRNAs were picked for further study. *In situ* hybridization confirmed that all 19 resided in MAP2-positive dendrites. Interestingly, a significant fraction of these mRNAs encoded molecules involved in translation, and several coimmunoprecipitated with the double-stranded RNA-binding protein Staufen, which has been implicated in RNA localization and translational regulation.

■ Behavioral/Systems/Cognitive

Sleepless in the Aquarium

David A. Prober, Jason Rihel, Anthony A. Onah, Rou-Jia Sung, and Alexander F. Schier

(see pages 13400–13410)

You'd think fish would not have that much on their minds to keep them up at night. But this week, Prober et al. describe transgenic zebrafish with a sleep disorder, a model system that may be useful in studies of sleep regulation. The authors first determined that hypocretin, the best

characterized sleep–wake regulator in mammals, is expressed in hypothalamic neurons of 5-d-old zebrafish in a pattern strikingly similar to that of mammals. The authors then engineered transgenic fish with a hypocretin promoter that could be induced by heat shock. Overexpression of the gene in zebrafish larvae promoted wakeful activity, hyperarousal, and inability to stay still, hallmarks of insomnia in humans. The effects of hypocretin overexpression were more dramatic in the absence of circadian cues, suggesting that the circadian system may normally antagonize hypocretin function.

◆ Neurobiology of Disease

Low Testosterone and Alzheimer Mice

Emily R. Rosario, Jenna C. Carroll, Salvatore Oddo, Frank M. LaFerla, and Christian J. Pike

(see pages 13384–13389)

Waning testosterone levels in aging men may be responsible for a slew of physical symptoms, dementia among them. Recent studies indicate that men with Alzheimer's disease (AD) have lower testosterone level than aged men without AD. Because the decline in testosterone concentrations precedes symptoms of AD, testosterone could increase the risk of disease development. Based on this evidence, Rosario et al. tested the relationship between testosterone and AD development using a triple transgenic mouse model of AD, which carries mutations in amyloid precursor protein, presenilin1, and tau. Castrating the transgenic mice at 3 months led to significant increases in the deposition of the β -amyloid ($A\beta$) peptide in the amygdala and the hippocampus after a 4 month interval. There were also associated behavioral deficits, indicating that complete androgen depletion can speed up AD-like pathology. These effects were prevented if the castrated mice were treated with androgen.

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Cover legend: Binding of a recombinant fragment of myosin-1c (Myo1c) (green), a component of the hair-cell transduction complex, to an isolated bullfrog saccular hair cell. Filamentous actin is stained in red to delineate the actin-filled stereocilia that comprise the mechanosensitive hair bundle. Note the intense binding of Myo1c to receptors at the tips of stereocilia, the site of hair-cell transduction, as well as binding within the soma. For more information, see the article by Phillips et al. in the October 18, 2006 issue (pages 10777–10788).

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Correction: In Figure 2B of the article "Cross-Modal Processing in Early Visual and Auditory Cortices depends on Expected Statistical Relationship of Multisensory Information" by Bernhard Baier, Andreas Kleinschmidt, and Notger G. Müller, which appears on pages 12260–12265 of the November 22, 2006 issue, the colors for the associated and non-associated conditions were switched.

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Neuron-Specific Conditional Expression of a Mitochondrially Targeted Fluorescent Protein in Mice

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Mitochondrial dysfunction contributes to the pathophysiology of both acute and chronic neurodegenerative disorders. Quantification of mitochondrial bioenergetic properties generally requires the use of isolated brain mitochondria. However, the involvement of neuronal mitochondrial dysfunction in these disorders is limited by the lack of markers, and therefore isolation procedures, that distinguish neuronal compared with astrocyte mitochondria. To address this and other issues concerning neuronal mitochondria in the CNS, transgenic mice were generated that express a fluorescent protein targeted specifically to neurons. A neuron-specific promoter, CaMKII α (calcium/calmodulin-dependent kinase II α) driven tTA (tetracycline transactivator) mice were crossed with TRE (tetracycline responsive element) driven mitochondrial targeted enhanced yellow fluorescent protein (eYFP) mice. Expression of eYFP in the bigenic mouse brain was observed only in neuronal mitochondria of striatum, forebrain, and hippocampus and was enhanced by the removal of the tetracycline analog doxycycline (Dox) in the diet. The respiratory control ratio of synaptic and nonsynaptic mitochondria isolated from eYFP-expressing mice was the same as control mice, suggesting that neuronal mitochondria expressing eYFP maintain normal bioenergetic functions. More importantly, the development of Dox-inducible, neuron targeted mito/eYFP transgenic mice offer a unique *in vivo* model for delineating the participation of neuronal mitochondria in neuronal survival and death.

The Journal of Neuroscience, December 20, 2006 • 26(51):13123–13127

Preference for Immediate over Delayed Rewards Is Associated with Magnitude of Ventral Striatal Activity

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Discounting future outcomes as a function of their deferred availability underlies much of human decision making. Discounting, or preference for immediate over delayed rewards of larger value, is often associated with impulsivity and is a risk factor for addictive disorders such as pathological gambling, cigarette smoking, and drug and alcohol abuse. The ventral striatum (VS) is involved in mediating behavioral responses and physiological states associated with reward, and dysregulation of the VS contributes to addiction, perhaps by affecting impulsive decision-making. Behavioral tests of delay discounting (DD), which index preference for smaller immediate over larger delayed rewards, covary with impulsive tendencies in humans. In the current study, we examined the relationship between individual differences in DD, measured in a behavioral assessment, and VS activity measured with blood oxygenation level-dependent functional magnetic resonance imaging, in 45 adult volunteers. VS activity was determined using a task involving positive and negative feedback with monetary reward. Analyses revealed that individual differences in DD correlate positively with magnitude of VS activation in response to both positive and negative feedback, compared with a no-feedback control condition. Variability in DD was also associated with differential VS activation in response to positive, compared with negative, feedback. Collectively, our results suggest that increased preference for smaller immediate over larger delayed rewards reflects both a relatively indiscriminate and hyper-reactive VS circuitry. They also highlight a specific neurocognitive mechanism that may contribute to increased risk for addiction.

The Journal of Neuroscience, December 20, 2006 • 26(51):13213–13217

Molecular Interaction between Projection Neuron Precursors and Invading Interneurons via Stromal-Derived Factor 1 (CXCL12)/CXCR4 Signaling in the Cortical Subventricular Zone/Intermediate Zone

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Most cortical interneurons are generated in the subpallial ganglionic eminences and migrate tangentially to their final destinations in the neocortex. Within the cortex, interneurons follow mainly stereotype routes in the subventricular zone/intermediate zone (SVZ/IZ) and in the marginal zone. It has been suggested that interactions between invading interneurons and locally generated projection neurons are implicated in the temporal and spatial regulation of the invasion process. However, so far experimental evidence for such interactions is lacking.

We show here that the chemokine stromal-derived factor 1 (SDF-1; CXCL12) is expressed in the main invasion route for cortical interneurons in the SVZ/IZ. Most SDF-1-positive cells are proliferating and express the homeodomain transcription factors Cux1 and Cux2. Using MASH-1 mutant mice in concert with the interneuron

marker DLX, we exclude that interneurons themselves produce the chemokine in an autocrine manner. We conclude that the SDF-1-expressing cell population represents the precursors of projection neurons during their transition and amplification in the SVZ/IZ. Using mice lacking the SDF-1 receptor CXCR4 or Pax6, we demonstrate that SDF-1 expression in the cortical SVZ/IZ is essential for recognition of this pathway by interneurons. These results represent the first evidence for a molecular interaction between precursors of projection neurons and invading interneurons during corticogenesis.

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Collapsin Response Mediator Protein 1 Mediates Reelin Signaling in Cortical Neuronal Migration

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Collapsin response mediator protein 1 (CRMP1) is one of the CRMP family members that mediates signal transduction of axon guidance molecules. Here, we show evidence that CRMP1 is involved in Reelin (Reln) signaling to regulate neuronal migration in the cerebral cortex. In *crmp1*^{-/-} mice, radial migration of cortical neurons was retarded. This phenotype was not observed in the *sema3A*^{-/-} and *crmp1*^{+/-};*sema3A*^{+/-} cortices. However, CRMP1 was colocalized with disabled-1 (Dab1), an adaptor protein in Reln signaling. In the *Reln*^{+/+} cortex, CRMP1 and Dab1 were expressed at a higher level, yet tyrosine phosphorylated at a lower level. Loss of *crmp1* in a *dab1* heterozygous background led to the disruption of hippocampal lamination, a Reeler-like phenotype. In addition to axon guidance, CRMP1 regulates neuronal migration by mediating Reln signaling.

The Journal of Neuroscience, December 20, 2006 • 26(51):13357–13362

Androgens Regulate the Development of Neuropathology in a Triple Transgenic Mouse Model of Alzheimer's Disease

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Normal age-related testosterone depletion in men is a recently identified risk factor for Alzheimer's disease (AD), but how androgen loss affects the development of AD is unclear. To investigate the relationship between androgen depletion and AD, we compared how androgen status affects the progression of neuropathology in the triple transgenic mouse model of AD (3xTg-AD). Adult male 3xTg-AD mice were sham gonadectomized (GDX) or GDX to deplete endogenous androgens and then exposed for 4 months to either the androgen dihydrotestosterone (DHT) or to placebo. In comparison to gonadally intact 3xTg-AD mice, GDX mice exhibited robust increases in the accumulation of β -amyloid ($A\beta$), the protein implicated as the primary causal factor in AD pathogenesis, in both hippocampus and amygdala. In parallel to elevated levels of $A\beta$, GDX mice exhibited significantly impaired spontaneous alternation behavior, indicating deficits in hippocampal function. Importantly, DHT treatment of GDX 3xTg-AD mice attenuated both $A\beta$ accumulation and behavioral deficits. These data demonstrate that androgen depletion accelerates the development of AD-like neuropathology, suggesting that a similar mechanism may underlie the increased risk for AD in men with low testosterone. In addition, our finding that DHT protects against acceleration of AD-like neuropathology predicts that androgen-based hormone therapy may be a useful strategy for the prevention and treatment of AD in aging men.

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Articles

NR3A Modulates the Outer Vestibule of the “NMDA” Receptor Channel

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Classical NMDA receptors (NMDARs), activated by glycine and glutamate, are heteromultimers comprised of NR1 and NR2 subunits. Coexpression of the novel NR3 family of NMDAR subunits decreases the magnitude of NR1/NR2 receptor-mediated currents or forms glycine-activated channels with the NR1 subunit alone. The second (M2) and third (M3) membrane segments of NR1 and NR2 subunits of classical NMDARs form the core of the channel permeation pathway. Structural information regarding NR1/NR3 channels remains unknown. Using the *Xenopus* oocyte expression system and the SCAM (substituted cysteine accessibility method), we found that M3 segments of both NR1 and NR3A form a narrow constriction in the outer vestibule of the channel, which prevents passage of externally applied sulfhydryl-specific agents. The most internal reactive residue in each M3 segment is the threonine in the conserved SYTANLAAF motif. These threonines appear to be symmetrically aligned. Several NR3A M3 mutations change the behavior of NR1/NR3A channels. Unlike NR1, however, the M3 segment of NR3A does not undergo extensive molecular rearrangement during channel gating by added glycine. Additionally, in the M2 segment, our data suggest that the amino acid at the asparagine (N) site of NR1, but not NR3A, contributes to the selectivity filter of NR1/3A channels. We therefore conclude that NR3A modulates the NR1/NR3A permeation pathway via a novel mechanism of forming a narrow constriction at the outer channel vestibule. This modified channel vestibule may also explain the dominant-negative effect of the NR3 subunit on channel behavior when coexpressed with NR1 and NR2 subunits.

The Journal of Neuroscience, December 20, 2006 • 26(51):13156–13166

Mechanisms of Efferent-Mediated Responses in the Turtle Posterior Crista

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To study the cellular mechanisms of efferent actions, we recorded from vestibular-nerve afferents close to the turtle posterior crista while efferent fibers were electrically stimulated. Efferent-mediated responses were obtained from calyx-bearing (CD, calyx and dimorphic) afferents and from bouton (B) afferents distinguished by their neuroepithelial locations into BT units near the torus and BM units at intermediate sites. The spike discharge of CD units is strongly excited by efferent stimulation, whereas BT and BM units are inhibited, with BM units also showing a postinhibitory excitation. Synaptic activity was recorded intracellularly after spikes were blocked. Responses of BT/BM units to single efferent shocks consist of a brief depolarization followed by a prolonged hyperpolarization. Both components reflect variations in hair-cell quantal release rates and are eliminated by pharmacological antagonists of $\alpha 9/\alpha 10$ nicotinic receptors. Blocking calcium-dependent SK potassium channels converts the biphasic response into a prolonged depolarization. Results can be explained, as in other hair-cell systems, by the sequential activation of $\alpha 9/\alpha 10$ and SK channels. In BM units, the postinhibitory excitation is based on an increased rate of hair-cell quanta and depends on the preceding inhibition. There is, in addition, an efferent-mediated, direct depolarization of BT/BM and CD fibers. In CD units, it is the exclusive efferent response. Nicotinic antagonists have different effects on hair-cell efferent actions and on the direct depolarization of CD and BT/BM units. Ultrastructural studies, besides confirming the efferent innervation of type II hair cells and calyx endings, show that turtle efferents commonly contact afferent boutons terminating on type II hair cells.

The Journal of Neuroscience, December 20, 2006 • 26(51):13180–13193

Connecden, A Novel DENN Domain-Containing Protein of Neuronal Clathrin-Coated Vesicles Functioning in Synaptic Vesicle Endocytosis

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Clathrin-coated vesicles (CCVs) are responsible for the endocytosis of multiple cargo, including synaptic vesicle membranes. We now describe a new CCV protein, termed *connecden*, that contains an N-terminal DENN (differentially expressed in neoplastic versus normal cells) domain, a poorly characterized protein module found in multiple proteins of unrelated function and a C-terminal peptide motif domain harboring three distinct motifs for binding the α -ear of the clathrin adaptor protein 2 (AP-2). *Connecden* coimmunoprecipitates and partially colocalizes with AP-2, and nuclear magnetic resonance and peptide competition studies reveal that all three α -ear-binding motifs contribute to AP-2 interactions. In addition, *connecden* contains multiple Src homology 3 (SH3) domain-binding motifs and coimmunoprecipitates with the synaptic SH3 domain proteins intersectin and endophilin A1. Interestingly, *connecden* is enriched on neuronal CCVs and is present in the presynaptic compartment of neurons. Moreover, *connecden* has a uniquely stable association with CCV membranes because it resists extraction with Tris and high-salt buffers, unlike most other CCV proteins, but it is not detected on purified synaptic vesicles. Together, these observations suggest that *connecden* functions on the endocytic limb of the synaptic vesicle cycle. Accordingly, disruption of *connecden* interactions with its binding partners through overexpression of the C-terminal peptide motif domain or knock down of *connecden* through lentiviral delivery of small hairpin RNA both lead to defects in synaptic vesicle endocytosis in cultured hippocampal neurons. Thus, we identified

connecden as a component of the endocytic machinery functioning in synaptic vesicle endocytosis, providing the first evidence of a role for a DENN domain-containing protein in endocytosis.

The Journal of Neuroscience, December 20, 2006 • 26(51):13202–13212

Ca²⁺ from One or Two Channels Controls Fusion of a Single Vesicle at the Frog Neuromuscular Junction

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Neurotransmitter release is triggered by the cooperative action of approximately five Ca²⁺ ions entering the presynaptic terminal through Ca²⁺ channels. Depending on the organization of the active zone (AZ), influx through one or many channels may be needed to cause fusion of a vesicle. Using a combination of experiments and modeling, we examined the number of channels that contribute Ca²⁺ for fusion of a single vesicle in a frog neuromuscular AZ. We compared Ca²⁺ influx to neurotransmitter release by measuring presynaptic action potential-evoked (AP-evoked) Ca²⁺ transients simultaneously with postsynaptic potentials. Ca²⁺ influx was manipulated by changing extracellular [Ca²⁺] (Ca_{ext}) to alter the flux per channel or by reducing the number of open Ca²⁺ channels with ω -conotoxin GVIA (ω -CTX). When Ca_{ext} was reduced, the exponent of the power relationship relating release to Ca²⁺ influx was 4.16 ± 0.62 (SD; $n = 4$), consistent with a biochemical cooperativity of ~ 5 . In contrast, reducing influx with ω -CTX yielded a power relationship of 1.7 ± 0.44 ($n = 5$) for Ca_{ext} of 1.8 mM and 2.12 ± 0.44 for Ca_{ext} of 0.45 mM ($n = 5$). Using geometrically realistic Monte Carlo simulations, we tracked Ca²⁺ ions as they entered through each channel and diffused in the terminal. Experimental and modeling data were consistent with two to six channel openings per AZ per AP; the Ca²⁺ that causes fusion of a single vesicle originates from one or two channels. Channel cooperativity depends mainly on the physical relationship between channels and vesicles and is insensitive to changes in the non-geometrical parameters of our model.

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c-Fos Facilitates the Acquisition and Extinction of Cocaine-Induced Persistent Changes

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Development of drug addiction involves persistent neurobiological changes. The dopamine D₁ receptor is involved in mediating cocaine-induced neuroadaptation, yet the underlying intracellular mechanisms remain unclear. We examined a potential role of the immediate early gene *Fos*, which is robustly and rapidly induced by cocaine via D₁ receptors, in mediating cocaine-induced persistent neurobiological changes by creating and analyzing a mouse in which *Fos* is primarily disrupted in D₁ receptor-expressing neurons in the brain. We show that the expression levels of several transcription factors, neurotransmitter receptors, and intracellular signaling molecules induced by repeated cocaine administration are altered in *Fos*-deficient brains. Dendritic remodeling of medium spiny neurons induced by repeated exposure to cocaine is blunted in the mutant mice. The mutant mice exhibit attenuated behavioral sensitization after repeated exposure to cocaine and more persistent memory of cocaine-induced conditioned place preference. Our findings indicate that c-Fos produced in D₁ receptor-expressing neurons integrates mechanisms to facilitate both the acquisition and extinction of cocaine-induced persistent changes.

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G-Proteins Modulate Cumulative Inactivation of N-Type (Ca_v2.2) Calcium Channels

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Precise regulation of N-type (Ca_v2.2) voltage-gated calcium channels (Ca-channels) controls many cellular functions including neurotransmitter and hormone release. One important mechanism that inhibits Ca²⁺ entry involves binding of G-protein $\beta\gamma$ subunits (G $\beta\gamma$) to the Ca-channels. This shifts the Ca-channels from “willing” to “reluctant” gating states and slows activation. Voltage-dependent reversal of the inhibition (facilitation) is thought to reflect transient dissociation of G $\beta\gamma$ from the Ca-channels and can occur during high-frequency bursts of action potential-like waveforms (APW). Inactivation of Ca-channels will also limit Ca²⁺ entry, but it remains unclear whether G-proteins can modulate inactivation. In part this is because of the complex nature of inactivation, and because facilitation of Ca-channel currents (*I_{Ca}*) masks the extent and kinetics of inactivation during typical stimulation protocols. We used low-frequency trains of APW to activate *I_{Ca}*. This more closely mimics physiological stimuli and circumvents the problem of facilitation which does not occur at ≤ 5 Hz. Activation of endogenous G-proteins reduced both Ca²⁺-dependent, and voltage-dependent inactivation of recombinant *I_{Ca}* in human embryonic kidney 293 cells. This was mimicked by expression of wild-type G $\beta\gamma$, but not by a point mutant of G $\beta\gamma$ with reduced affinity for Ca-channels. A similar decrease in the inactivation of *I_{Ca}* was produced by P2Y receptors in adrenal chromaffin cells. Overall, our data identify and characterize a novel effect of G-proteins on *I_{Ca}*, and could have important implications for understanding how G-protein-coupled receptors control Ca²⁺ entry and Ca²⁺-dependent events such as neurotransmitter and hormone release.

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Deletion of the *Ttf1* Gene in Differentiated Neurons Disrupts Female Reproduction without Impairing Basal Ganglia Function

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Thyroid transcription factor 1 (TTF1) [also known as Nkx2.1 (related to the NK-2 class of homeobox genes) and T/ebp (thyroid-specific enhancer-binding protein)], a homeodomain gene required for basal forebrain morphogenesis, remains expressed in the hypothalamus after birth, suggesting a role in neuroendocrine function. Here, we show an involvement of TTF1 in the control of mammalian puberty and adult reproductive function. Gene expression profiling of the nonhuman primate hypothalamus revealed that TTF1 expression increases at puberty. Mice in which the *Ttf1* gene was ablated from differentiated neurons grew normally and had normal basal ganglia/hypothalamic morphology but exhibited delayed puberty, reduced reproductive capacity, and a short reproductive span. These defects were associated with reduced hypothalamic expression of genes required for sexual development and deregulation of a gene involved in restraining puberty. No extrapyramidal impairments associated with basal ganglia dysfunction were apparent. Thus, although TTF1 appears to fulfill only a morphogenic function in the ventral telencephalon, once this function is satisfied in the hypothalamus, TTF1 remains active as part of the transcriptional machinery controlling female sexual development.

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Brain-Derived Neurotrophic Factor Participates in Determination of Neuronal Laminal Fate in the Developing Mouse Cerebral Cortex

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Lamina formation in the developing cerebral cortex requires precisely regulated generation and migration of the cortical progenitor cells. To test the possible involvement of brain-derived neurotrophic factor (BDNF) in the formation of the cortical lamina, we investigated the effects of BDNF protein and anti-BDNF antibody separately administered into the telencephalic ventricular space of 13.5-d-old mouse embryos. BDNF altered the position, gene-expression properties, and projections of neurons otherwise destined for layer IV to those of neurons for the deeper layers, V and VI, of the cerebral cortex, whereas anti-BDNF antibody changed some of those of neurons of upper layers II/III. Additional analysis revealed that BDNF altered the laminar fate of neurons only if their parent progenitor cells were exposed to it at approximately S-phase and that it hastened the timing of the withdrawal of their daughter neurons from the ventricular proliferating pool by accelerating the completion of S-phase, downregulation of the Pax6 (paired box gene 6) expression, an essential transcription factor for generation of the upper layer neurons, and interkinetic nuclear migration of cortical progenitors in the ventricular zone. These observations suggest that BDNF participates in the processes forming the neuronal laminas in the developing cerebral cortex. BDNF can therefore be counted as one of the key extrinsic factors that regulate the laminar fate of cortical neurons.

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Primary Afferent Synapses on Developing and Adult Renshaw Cells

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The mechanisms that diversify adult interneurons from a few pools of embryonic neurons are unknown. Renshaw cells, Ia inhibitory interneurons (IaINs), and possibly other types of mammalian spinal interneurons have common embryonic origins within the V1 group. However, in contrast to IaINs and other V1-derived interneurons, adult Renshaw cells receive motor axon synapses and lack proprioceptive inputs. Here, we investigated how this specific pattern of connectivity emerges during the development of Renshaw cells. Tract tracing and immunocytochemical markers [parvalbumin and vesicular glutamate transporter 1 (VGLUT1)] showed that most embryonic (embryonic day 18) Renshaw cells lack dorsal root inputs, but more than half received dorsal root synapses by postnatal day 0 (P0) and this input spread to all Renshaw cells by P10–P15. Electrophysiological recordings in neonates indicated that this input is functional and evokes Renshaw cell firing. VGLUT1-IR bouton density on Renshaw cells increased until P15 but thereafter decreased because of limited synapse proliferation coupled with the enlargement of Renshaw cell dendrites. In parallel, Renshaw cell postsynaptic densities apposed to VGLUT1-IR synapses became smaller in adult compared with P15. In contrast, vesicular acetylcholine transporter-IR motor axon synapses contact embryonic Renshaw cells and proliferate postnatally matching Renshaw cell growth. Like other V1 neurons, Renshaw cells are thus competent to receive sensory synapses. However, after P15, these sensory inputs appear deselected through arrested proliferation and synapse weakening. Thus, Renshaw cells shift from integrating sensory and motor inputs in neonates to predominantly motor inputs in adult. Similar synaptic weight shifts on interneurons may be involved in the maturation of motor reflexes and locomotor circuitry.

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Netrin/DCC Signaling Controls Contralateral Dendrites of Octavolateralis Efferent Neurons

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The guidance molecule Netrin and its receptor DCC (deleted in colorectal cancer) attract commissural axons toward the midline en route to their final destination. To test whether these molecules can also guide dendrites, we studied the contralateral dendrites of zebrafish octavolateralis efferent (OLE) neurons, which are unusual in that they navigate toward and cross the midline. We found that, at the time of dendrite outgrowth, OLE neurons express *dcc*, and the hindbrain midline expresses *netrin1*. Knocking down *dcc* or *netrin1* function by injecting antisense morpholino oligonucleotides prevented OLE contralateral dendrites from crossing the midline, showing that *dcc* and *netrin1* are necessary for dendrite guidance or formation. Furthermore, by transplanting cells from *dcc* morphants into wild-type embryos and vice versa, we demonstrated that *dcc* acts cell autonomously in OLE dendrites. This work is the first evidence that Netrin/DCC signaling acts in dendrites in a vertebrate system.

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An Essential Role for the Integrin-Linked Kinase–Glycogen Synthase Kinase-3 β Pathway during Dendrite Initiation and Growth

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Multiple cues, including growth factors and circuit activity, signal to regulate the initiation and growth of mammalian dendrites. In this study, we have asked how these environmental cues regulate dendrite formation, and in particular, whether dendrite initiation and growth requires integrin-linked kinase (ILK) or its downstream effector, glycogen synthase kinase-3 β (GSK-3 β). In cultured sympathetic neurons, NGF and neuronal depolarization activated ILK and promoted dendrite initiation and growth, and inhibition of ILK (either pharmacologically, with a dominant-negative form of ILK, or by genetic knockdown) reduced depolarization-induced dendrite formation. In sympathetic neurons, ILK phosphorylated and inhibited GSK-3 β , and inhibition of GSK-3 β (either pharmacologically, with dominant-negative GSK-3 β , or by genetic knockdown) caused robust dendrite initiation. GSK-3 β inhibition also caused dendrite initiation in cultured cortical neurons and growth of hippocampal neurons in slice cultures. GSK-3 β functioned downstream of ILK to regulate dendrite formation, because inhibition of GSK-3 β promoted dendrite initiation even when ILK was simultaneously inhibited. Moreover, GSK-3 β promoted dendrite formation in sympathetic neurons by regulating the activity of a key dendrite formation effector, the MAP (microtubule-associated protein) kinase kinase (MEK)–extracellular signal-regulated protein kinase (ERK) pathway. Specifically, inhibition of GSK-3 β led to increased ERK phosphorylation, and inhibition of MEK completely blocked the effects of GSK-3 β inhibition on dendrite initiation and growth. Thus, the ILK–GSK-3 β pathway plays a key role in regulating dendrite formation in developing mammalian neurons.

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Identification of Process-Localized mRNAs from Cultured Rodent Hippocampal Neurons

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The regulated translation of localized mRNAs in neurons provides a mechanism for spatially restricting gene expression in a synapse-specific manner. To identify the population of mRNAs present in distal neuronal processes of rodent hippocampal neurons, we grew neurons on polycarbonate filters etched with 3 μ m pores. Although the neuronal cell bodies remained on the top surface of the filters, dendrites, axons, and glial processes penetrated through the pores to grow along the bottom surface of the membrane where they could be mechanically separated from cell bodies. Quantitative PCR and immunochemical analyses of the process preparation revealed that it was remarkably free of somatic contamination. Microarray analysis of RNA isolated from the processes identified over 100 potentially localized mRNAs. *In situ* hybridization studies of 19 of these transcripts confirmed that all 19 were present in dendrites, validating the utility of this approach for identifying dendritically localized transcripts. Many of the identified mRNAs encoded components of the translational machinery and several were associated with the RNA-binding protein Staufen. These findings indicate that there is a rich repertoire of mRNAs whose translation can be locally regulated and support the emerging idea that local protein synthesis serves to boost the translational capacity of synapses.

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Two Retinotopic Visual Areas in Human Lateral Occipital Cortex

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We describe two visual field maps, lateral occipital areas 1 (LO1) and 2 (LO2), in the human lateral occipital cortex between the dorsal part of visual area V3 and visual area V5/MT+. Each map contained a topographic representation of the contralateral visual hemifield. The eccentricity representations were shared with V1/V2/V3. The polar angle representation in LO1 extended from the lower vertical meridian (at the boundary with dorsal V3) through the horizontal to the upper vertical meridian (at the boundary with LO2). The polar angle representation in LO2 was the mirror-reversal of that in LO1. LO1 and LO2 overlapped with the posterior part of the object-selective lateral occipital complex and the kinetic occipital region (KO). The retinotopy and functional properties of LO1 and LO2 suggest that they correspond to two new human visual areas, which lack exact homologues in macaque visual cortex. The topography, stimulus selectivity, and anatomical location of LO1 and LO2 indicate that they integrate shape information from multiple visual submodalities in retinotopic coordinates.

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Apparent Encoding of Sequential Context in Rat Medial Prefrontal Cortex Is Accounted for by Behavioral Variability

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Simple sequences can be represented via asymmetrically linked neural assemblies, provided that the elements of the sequence are unique. When elements repeat, however (e.g., A-B-C-B-A), the same element belongs to two separate “sequential contexts,” and a more complex encoding mechanism is required. To enable correct sequence performance, some neural structure must provide a disambiguating signal that differentiates the two sequential contexts (i.e., B as an element of “A-B” as opposed to “C-B”). The disambiguating signal may derive from a form of working memory, or, in some cases, a simple timing mechanism may suffice. To investigate the possible role of medial prefrontal cortex in complex sequence encoding, rats were trained on a spatial sequence containing two adjacent repeated segments (e.g., A-B-C-D-B-C-E). The double-repeat procedure minimized behavioral differences in the second leg (C) of the repeat subsequence that arise in the first leg (B) because of differences in the entry point (e.g., A-B vs D-B). Far more cells were context sensitive along the first leg than along the second (36 vs 9%), and most of the differences were accounted for by systematic variations in the rat’s trajectory, which were much larger along the first leg. There is thus little evidence for sequential context-discriminative activity in the medial prefrontal cortex that cannot plausibly be accounted for by context-dependent behavior. The finding that the rodent medial prefrontal cortex is highly sensitive to sensory-behavioral variables raises doubts about previous experiments that purport to show working memory-related activity in this region.

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Modulation of Neural Activity during Observational Learning of Actions and Their Sequential Orders

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How does the brain transform perceptual representations of others’ actions into motor representations that can be used to guide behavior? Here we used functional magnetic resonance imaging to record human brain activity while subjects watched others construct multipart objects under varied task demands. We find that relative to resting baseline, passive action observation increases activity within inferior frontal and parietal cortices implicated in action encoding (mirror system) and throughout a distributed network of areas involved in motor representation, including dorsal premotor cortex, pre-supplementary motor area, cerebellum, and basal ganglia (experiments 1 and 2). Relative to passive observation, these same areas show increased activity when subjects observe with the intention to subsequently reproduce component actions using the demonstrated sequential procedures (experiment 1). Observing the same actions with the intention of reproducing component actions, but without the requirement to use the demonstrated sequential procedure, increases activity in the same regions, although to a lesser degree (experiment 2). These findings demonstrate that when attempting to learn behaviors through observation, the observers’ intentions modulate responses in a widely distributed network of cortical and subcortical regions implicated previously in action encoding and/or motor representation. Among these regions, only activity within the right intraparietal sulcus predicts the accuracy with which observed procedures are subsequently performed. Successful formation of motor representations of sequential procedures through observational learning is dependent on computations implemented within this parietal region.

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Neural Correlates of Vibrotactile Working Memory in the Human Brain

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Recent neurophysiological studies in macaques identified a network of brain regions related to vibrotactile working memory (WM), including somatosensory, motor, premotor, and prefrontal cortex. In these studies, monkeys decided which of two vibrotactile stimuli that were sequentially applied to their fingertips and separated by a short delay had the higher vibration frequency. Using the same task, the objective of the present study was to identify the neural correlates related to the different task periods (encoding, maintenance, and decision making) of vibrotactile WM in the human brain. For this purpose, we used event-related functional magnetic resonance imaging and contrasted WM trials with a control condition of vibrotactile stimulation that did not require maintenance and decision making. We found that vibrotactile WM has a similar but not identical neural organization in humans and monkeys. Consistent with neurophysiological data in monkeys and behavioral studies in humans, the primary somatosensory and the ventral premotor cortex exhibited increased activity during encoding. Maintenance of a vibrotactile memory trace evoked activity in the premotor and ventrolateral prefrontal cortex. Decision making caused activation in the somatosensory, premotor, and lateral prefrontal cortex. However, human vibrotactile WM recruited additional areas. Decision making activated a broader network than that studied thus far in monkeys. Maintenance and decision making additionally activated the inferior parietal lobe. Although the different task components evoked activity in distinctive neural networks, there was considerable overlap of activity, especially regarding maintenance and decision making, indicating that similar neural mechanisms are required for the subprocesses related to these task components.

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Local Edge Detectors: A Substrate for Fine Spatial Vision at Low Temporal Frequencies in Rabbit Retina

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Visual acuity is limited by the size and density of the smallest retinal ganglion cells, which correspond to the midget ganglion cells in primate retina and the β -ganglion cells in cat retina, both of which have concentric receptive fields that respond at either light-On or light-Off. In contrast, the smallest ganglion cells in the rabbit retina are the local edge detectors (LEDs), which respond to spot illumination at both light-On and light-Off. However, the LEDs do not predominate in the rabbit retina and the question arises, what role do they play in fine spatial vision? We studied the morphology and physiology of LEDs in the isolated rabbit retina and examined how their response properties are shaped by the excitatory and inhibitory inputs. Although the LEDs comprise only ~15% of the ganglion cells, neighboring LEDs are separated by 30–40 μm on the visual streak, which is sufficient to account for the grating acuity of the rabbit. The spatial and temporal receptive-field properties of LEDs are generated by distinct inhibitory mechanisms. The strong inhibitory surround acts presynaptically to suppress both the excitation and the inhibition elicited by center stimulation. The temporal properties, characterized by sluggish onset, sustained firing, and low bandwidth, are mediated by the temporal properties of the bipolar cells and by postsynaptic interactions between the excitatory and inhibitory inputs. We propose that the LEDs signal fine spatial detail during visual fixation, when high temporal frequencies are minimal.

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Previous Experience with Behavioral Control over Stress Blocks the Behavioral and Dorsal Raphe Nucleus Activating Effects of Later Uncontrollable Stress: Role of the Ventral Medial Prefrontal Cortex

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Previous experience with stressors over which the subject has behavioral control blocks the typical behavioral consequences of subsequent exposure to stressors over which the organism has no behavioral control. The present experiments explored the involvement of the ventral medial prefrontal cortex (mPFCv) in mediating this “immunizing” or resilience producing effect of an initial experience with control. Behavioral immunization was blocked by inactivation of the mPFCv with muscimol at the time of the initial experience with control, as well as at the time of the later exposure to uncontrollable stress. Inhibition of protein synthesis within the mPFCv by anisomycin also blocked immunization when administered at the time of the initial controllable stress but had no effect when administered at the time of the later uncontrollable stress. Additional experiments found that the initial experience with control blocks the intense activation of serotonergic cells in the dorsal raphe nucleus that would normally be produced by uncontrollable stress, providing a mechanism for behavioral immunization. Furthermore, mPFCv activity during the initial controllable stressor was required for this effect to occur. These results suggest that the mPFCv is needed both to process information about the controllability of stressors and to utilize such information to regulate responses to subsequent stressors. Moreover, the mPFCv may be a site of storage or plasticity concerning controllability information. These results are consistent with recent research in other domains that explore the functions of the mPFCv.

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The Fate of Old Memories after Medial Temporal Lobe Damage

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Damage to the hippocampal region and related medial temporal lobe structures (perirhinal, entorhinal, and parahippocampal cortices) impairs new learning (anterograde amnesia) as well as memory for information that was acquired before the damage occurred (retrograde amnesia). We assessed retrograde amnesia with the Autobiographical Memory Interview (AMI) and with a news events test in six patients with damage limited primarily to the hippocampal region (H group) and two patients with large medial temporal lobe lesions (MTL group). On the news event test, the H group exhibited temporally limited retrograde amnesia covering ~5 years. On the same test, the MTL group exhibited an extensive retrograde amnesia covering decades. Nevertheless, performance was relatively spared for very remote time periods. On the AMI, all patients had intact remote autobiographical memory. Because our patients with hippocampal lesions, as well as our patients with large MTL lesions, performed normally on the AMI, patients who perform poorly on the same test presumably have damage beyond the hippocampus and related structures in the medial temporal lobe. The findings emphasize the difference in the extent of retrograde amnesia associated with hippocampal lesions and large MTL lesions.

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Brain Connectivity Related to Working Memory Performance

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Several brain areas show signal decreases during many different cognitive tasks in functional imaging studies, including the posterior cingulate cortex (PCC) and a medial frontal region incorporating portions of the medial frontal gyrus and ventral anterior cingulate cortex (MFG/vACC). It has been suggested that these areas are components in a default mode network that is engaged during rest and disengaged during cognitive tasks. This study investigated the functional connectivity between the PCC and MFG/vACC during a working memory task and at rest by examining temporal correlations in magnetic resonance signal levels between the regions. The two regions were functionally connected in both conditions. In addition, performance on the working memory task was positively correlated with the strength of this functional connection not only during the working memory task, but also at rest. Thus, it appears these regions are components of a network that may facilitate or monitor cognitive performance, rather than becoming disengaged during cognitive tasks. In addition, these data raise the possibility that the individual differences in coupling strength between these two regions at rest predict differences in cognitive abilities important for this working memory task.

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Cross-Whisker Adaptation of Neurons in the Rat Barrel Cortex

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Neurons in the barrel cortex and the thalamus respond preferentially to stimulation of one whisker (the principal whisker) and weakly to several adjacent whiskers. Cortical neurons, unlike thalamic cells, gradually adapt to repeated whisker stimulations. Whether cortical adaptation is specific to the stimulated whisker is not known. The aim of this intracellular study was to determine whether the response of a cortical cell to stimulation of an adjacent whisker would be affected by previous adaptation induced by stimulation of the principal whisker and vice versa. Using a high-frequency stimulation that causes substantial adaptation in the cortex and much less adaptation in the thalamus, we show that cortical adaptation evoked by a train of stimuli applied to one whisker does not affect the synaptic response to subsequent stimulation of a neighboring whisker. Our data indicate that intrinsic mechanisms are not involved in cortical adaptation. Thalamic recordings obtained under the same conditions demonstrated that an adjacent whisker response was not generated in the thalamus, indicating that the observed whisker-specific adaptation results from diverging thalamic inputs or from cortical integration.

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Hypocretin/Orexin Overexpression Induces An Insomnia-Like Phenotype in Zebrafish

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As many as 10% of humans suffer chronic sleep disturbances, yet the genetic mechanisms that regulate sleep remain essentially unknown. It is therefore crucial to develop simple and cost-effective vertebrate models to study the genetic regulation of sleep. The best characterized mammalian sleep/wake regulator is hypocretin/orexin (Hcrt), whose loss results in the sleep disorder narcolepsy and that has also been implicated in feeding behavior, energy homeostasis, thermoregulation, reward seeking, addiction, and maternal behavior. Here we report that the expression pattern and axonal projections of embryonic and larval zebrafish Hcrt neurons are strikingly similar to those in mammals. We show that zebrafish larvae exhibit robust locomotive sleep/wake behaviors as early as the fifth day of development and that Hcrt overexpression promotes and consolidates wakefulness and inhibits rest. Similar to humans with insomnia, Hcrt-overexpressing larvae are hyperaroused and have dramatically reduced abilities to initiate and maintain rest at night. Remarkably, Hcrt function is modulated by but does not require normal circadian oscillations in locomotor activity. Our zebrafish model

of Hcrt overexpression indicates that the ancestral function of Hcrt is to promote locomotion and inhibit rest and will facilitate the discovery of neural circuits, genes, and drugs that regulate Hcrt function and sleep.

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NEUROBIOLOGY OF DISEASE

Subcutaneous Nogo Receptor Removes Brain Amyloid- β and Improves Spatial Memory in Alzheimer's Transgenic Mice

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The production and aggregation of cerebral amyloid- β (A β) peptide are thought to play a causal role in Alzheimer's disease (AD). Previously, we found that the Nogo-66 receptor (NgR) interacts physically with both A β and the amyloid precursor protein (APP). The inverse correlation of A β levels with NgR levels within the brain may reflect regulation of A β production and/or A β clearance. Here, we assess the potential therapeutic benefit of peripheral NgR-mediated A β clearance in APP^{swe}/PSEN-1 Δ E9 transgenic mice. Through site-directed mutagenesis, we demonstrate that the central 15–28 aa of A β associate with specific surface-accessible patches on the leucine-rich repeat concave side of the solenoid structure of NgR. In transgenic mice, subcutaneous NgR(310)ecto-Fc treatment reduces brain A β plaque load while increasing the relative levels of serum A β . These changes in A β are correlated with improved spatial memory in the radial arm water maze. The benefits of peripheral NgR administration are evident when therapy is initiated after disease onset. Thus, the peripheral association of NgR(310)ecto-Fc with central A β residues provides an effective therapeutic approach for AD.

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Analgesic Effects of Fatty Acid Amide Hydrolase Inhibition in a Rat Model of Neuropathic Pain

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Cannabinoid-based medicines have therapeutic potential for the treatment of pain. Augmentation of levels of endocannabinoids with inhibitors of fatty acid amide hydrolase (FAAH) is analgesic in models of acute and inflammatory pain states. The aim of this study was to determine whether local inhibition of FAAH alters nociceptive responses of spinal neurons in the spinal nerve ligation model of neuropathic pain. Electrophysiological studies were performed 14–18 d after spinal nerve ligation or sham surgery, and the effects of the FAAH inhibitor cyclohexylcarbamic acid 3-carbamoyl biphenyl-3-yl ester (URB597) on mechanically evoked responses of spinal neurons and levels of endocannabinoids were determined.

Intraplantar URB597 (25 μ g in 50 μ l) significantly ($p < 0.01$) attenuated mechanically evoked responses of spinal neurons in sham-operated rats. Effects of URB597 were blocked by the cannabinoid 1 receptor (CB₁) antagonist AM251 [*N*-1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-*N*-1-piperidinyl-1-*H*-pyrazole-3-carboxamide] (30 μ g in 50 μ l) and the opioid receptor antagonist naloxone. URB597 treatment increased levels of anandamide, 2-arachidonyl glycerol, and oleoyl ethanolamide in the ipsilateral hindpaw of sham-operated rats. Intraplantar URB597 (25 μ g in 50 μ l) did not, however, alter mechanically evoked responses of spinal neurons in spinal nerve ligated (SNL) rats or hindpaw levels of endocannabinoids. Intraplantar injection of a higher dose of URB597 (100 μ g in 50 μ l) significantly ($p < 0.05$) attenuated evoked responses of spinal neurons in SNL rats but did not alter hindpaw levels of endocannabinoids. Spinal administration of URB597 attenuated evoked responses of spinal neurons and elevated levels of endocannabinoids in sham-operated and SNL rats. These data suggest that peripheral FAAH activity may be altered or that alternative pathways of metabolism have greater importance in SNL rats.

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