This Week in The Journal

Cellular/Molecular

Another Role for the M Current
Jérôme J. Devaux, Kleopas A. Kleopa, Edward C. Cooper, and Steven S. Scherer
(see pages 1236–1244)

The subunits underlying the M current, a subthreshold potassium current first described in sympathetic neurons and pyramidal cells, evaded identification until the discovery of the KCNQ family a few years ago. KCNQ mutations are associated with several diseases, including epilepsy, hearing loss, and most recently, myokymia, a worm-like, repetitive movement of muscles thought to be attributable to axonal hyperexcitability. Devaux et al. now reveal expression of KCNQ2 in a location that might help explain these effects on neuronal excitability: initial segments and nodes of Ranvier in peripheral and central neurons. Aware of a slowly activating, M-like current at nodes, the authors searched for KCNQ subunits. They found KCNQ2 channels at nodes and initial segments, along with voltage-dependent sodium channels, and ankyrin-G, a cytoskeletal linker protein. KCNQ3 channels, in contrast, were expressed in a more diffuse, nonoverlapping pattern. The channels were seen only in nonfixed neurons, perhaps explaining past failures to detect the channels in nodes.

KCNQ2 (red) localizes to the axonal membrane at a node of Ranvier as seen in this single confocal section. The neurofilament protein, NF-H (green) marks the axonal cytoplasm.

Behavioral/Systems/Cognitive

Premotor Cortex Pathways that Shape the Hand
H. Shimazu, M. A. Maier, G. Cerri, P. A. Kirkwood, and R. N. Lemon
(see pages 1200–1211)

Area F5 of the ventral premotor cortex is involved in the sensorimotor transformation that allows visually guided control of hand shape in activities such as grasping. Disruption of F5 activity interferes with hand grasping, and direct stimulation of F5 can evoke hand movements. Now Shimazu et al. examine whether F5 influences hand shape through direct connections to spinal cord or through cortico-cortical connections to primary motor cortex (M1). In anesthetized monkeys, stimulation of microelectrodes implanted in F5 did not produce direct corticospinal activity, although pairs of shocks did produce small, longer-latency (“indirect”) activity. Conditioning shocks to F5, however, facilitated M1-stimulated indirect corticospinal activity as well as EPSPs in hand motor neurons. The results point to an excitatory influence of area F5 on M1, presumably via activation of interneuronal networks in M1. The authors suggest that this mechanism may parallel the positive gain control of smooth pursuit eye movements mediated by frontal pursuit areas.

Neurobiology of Disease

The Timing of Stroke Rehab in the Rat
Jeff Biernaskie, Garry Chernenko, and Dale Corbett
(see pages 1245–1254)

Clinicians know that strokes generally cause maximum functional deficits within a day or two of onset, followed often by gradual improvement that plateaus after a month or so. Although rehabilitation has many benefits, its effect on objective neurological recovery is difficult to measure in patients. In this issue, Biernaskie et al. investigated when rehabilitative training has the greatest impact. The authors occluded a middle cerebral artery (MCA) in rats to produce focal ischemia, followed by 5 weeks of rehabilitation at 5, 14, or 30 d after infarct. What is “rehab” in a rat? Well, cage objects were used to stimulate bimanual limb use, and reaching tasks encouraged use of the affected limb with mini M&Ms as the reward! Only the early treatment improved functional recovery. Interestingly, early rehab was also associated with increased length and branching of dendrites in layer V motor cortex in the undamaged hemisphere, indicating a possible role of rehabilitation on compensatory recruitment and remodeling.

Making Renshaw Cells
Tamar Sapir, Eric J. Geiman, Zhi Wang, Tomoko Velasquez, Sachiko Mitsui, Yoshihiro Yoshihara, Eric Frank, Francisco J. Alvarez, and Martyn Goulding
(see pages 1255–1264)

The Renshaw cell of the ventral spinal cord was the first physiologically identified interneuron, providing recurrent inhibition onto motor neurons. Now Sapir et al. reveal a bit of the path leading to Renshaw cell development. The neuronal circuits that control posture and locomotion in the ventral spinal cord arise from five embryonic precursors: motor neurons and four interneuron subtypes (V0–V3). In an effort to match up these embryonic interneurons with their mature fate, Sapir et al. concentrated on the V1 class. They first identified differentiated progeny of V1 cells expressing the En1 transcription factor, and determined that a subset of these were Renshaw cells. They then examined mice deficient in either of two transcription factors, Pax6 and En1. Pax6-deficient mice lacked Renshaw cells, whereas En1-deficient mice had Renshaw cells with fewer recurrent connections onto motor neurons, suggesting roles at different stages in Renshaw cell development.
Five Ca²⁺/H¹¹⁰⁰₁ syntillas (from scintilla, L. spark, in a synaptic structure, a nerve terminal) as imaged using the Ca²⁺ indicator fluo-3 in the cytosol of an isolated terminal from a single mouse hypothalamic neuron. Each panel shows a single syntilla, all arising in the same terminal. The circular outline of the terminal can be seen on the square blue background. Syntillas arise from intraterminal Ca²⁺ stores, are mediated by ryanodine receptors, and are increased in frequency by physiological levels of depolarization in the absence of Ca²⁺ influx. The diameter of the nerve terminal is 8 μm. For details, see the article by De Crescenzo et al. in this issue (pages 1226 –1235).
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**Correction:** In the article "Apamin-Sensitive Small Conductance Calcium-Activated Potassium Channels, through their Selective Coupling to Voltage-Gated Calcium Channels, Are Critical Determinants of the Precision, Pace, and Pattern of Action Potential Generation in Rat Subthalamic Nucleus Neurons In Vitro," by Nicholas E. Hallworth, Charles J. Wilson, and Mark D. Bevan, which appeared on pages 7525–7542 of the August 20, 2003 issue, the following corrections should be noted: (1) Dr. Bevan is affiliated with both the first and third institutions listed (1University of Tennessee, Anatomy and Neurobiology, Memphis, Tennessee 38163, and 3Department of Physiology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois 60611-3008). (2) The second sentence of the abstract should read: “To determine how such patterns of activity are regulated by small conductance potassium (SK)/calcium-activated potassium (KCa) channels and voltage-gated calcium (CaV) channels, STN neurons were recorded in the perforated patch configuration in slices [which were prepared from postnatal day 16 (P16)–P30 rats and held at 37°C] and then treated with the SK KCa channel antagonist apamin or the SK KCa channel agonist 1-ethyl-2-benzimidazolinone or the CaV channel antagonists g-conotoxin GVIA (CaV2.2-selective) or nifedipine (CaV1.2-1.3-selective).” (3) The sentence beginning on line 7 of page 7526 should read “In recent whole-cell patch clamp recording studies of STN neurons, calcium entry via voltage-gated calcium (CaV) channels predominantly activated small conductance potassium (SK)/calcium-activated potassium (KCa) channels, which played a pivotal, largely suppressive role in shaping activity or activated nonspecific cation channels, which augmented activity (Bevan and Wilson, 1999; Beurrier et al., 1999, 2000; Otsuka et al., 2001).” (4) The second sentence of the legend to Figure 10 should read: “A, B, Combined fluorescent and electrical recordings of subthreshold and suprathreshold rebound responses in an STN neuron (inset).” (5) In the Discussion, the sentence starting on line 8 of the third paragraph should read: “Indeed, SK KCa channel or CaV2.2 channel blockade increased firing rates in response to equivalent input but did not disrupt the pattern of driven activity.”

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The Discovery and Characterization of a Proton-Gated Sodium Current in Rat Retinal Ganglion Cells

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The conduction of acid-evoked currents in central and sensory neurons is now primarily attributed to a family of proteins called acid-sensing ion channels (ASICs). In peripheral neurons, their physiological function has been linked to nociception, mechanoreception, and taste transduction; however, their role in the CNS remains unclear. This study describes the discovery of a proton-gated current in rat retinal ganglion cells termed $I_{Na(H)}$, which also appears to be mediated by ASICs. RT-PCR confirmed the presence of ASIC mRNA (subunits la, 2a, 2b, 3, and 4) in the rat retina. Electrophysiological investigation showed that all retinal ganglion cells respond to rapid extracellular acidification with the activation of a transient $Na^+$ current, the size of which increases with increasing acidification between pH 6.5 and pH 3.0. $I_{Na(H)}$ desensitizes completely in the continued presence of acid, its current–voltage relationship is linear and its reversal potential shifts with pH. $I_{Na(H)}$ is reversibly inhibited by amiloride ($IC_{50}$ 188 μM) but is resistant to block by TTX (0.5 μM), Cd $^{2+}$ (100 μM), procaine (10 μM), and is not activated by capsaicin (0.5 μM). $I_{Na(H)}$ is not potentiated by Zn $^{2+}$ (300 μM) or AQ: APhe-Met-Arg-Phe-amide (50 μM) but is inhibited by neuropeptide-FF (50 μM). Acute application of pH 6.5 to retinal ganglion cells causes sustained depolarization and repetitive firing similar to the trains of action potentials normally associated with current injection into these cells. The presence of a proton-gated current in the neural retina suggests that ASICs may have a more diverse role in the CNS.

Activity-Dependent Expression of Acyl-Coenzyme A-Binding Protein in Retinal Muller Glian Cells Evoked by Optokinetic Stimulation

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Long-term horizontal optokinetic stimulation (HOKS) decreases the gain of the horizontal optokinetic reflex and evokes the second phase of optokinetic afternystagmus (OKAN-II). We investigated the possible molecular constituents of this adaptation. We used a differential display reverse transcriptase-PCR screen for mRNAs isolated from retinas of rabbits that received HOKS. In each rabbit, we compared mRNAs from the retina stimulated in the posterior—null direction. ACBP was localized to Muller glial cells by hybridization histochemistry and by immunohistochemistry. ACBP interacts with the $\alpha_1$-subunit of the GABA$_A$ receptor, as determined by a yeast two-hybrid technique. This interaction was confirmed by immuno precipitation of ACBP and the $\alpha_1$-subunit of the GABA$_A$ receptor using an antibody to GABA$_A$-$\alpha_1$. The interaction was also confirmed by a “pull-down” assay in which histidine-tagged ACBP was used to pull down $\alpha_1$. HOKS-treated expression of ACBP could provide a molecular basis for adaptation to HOKS and for the genesis of OKAN-II.

Nuclear Factor E2-Related Factor 2-Dependent Antioxidant Response Element Activation by tert-Butylhydroquinone and Sulforaphane Occurring Preferentially in Astrocytes Conditions Neurons against Oxidative Insult

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Binding of the transcription factor nuclear factor E2-related factor 2 (Nrf2) to the antioxidant response element (ARE) in neural cells results in the induction of a battery of genes that can coordinate a protective response against a variety of oxidative stressors. In this study, tert-butylhydroquinone (tBHQ) and sulforaphane were used as activators of this pathway. Consistent with previous studies, treatment of primary cortical cultures from ARE reporter mice revealed selective promoter activity in astrocytes. This activation protected neurons from hydrogen peroxide and nonexcitotoxic glutamate toxicity. tBHQ treatment of cultures from Nrf2 knockout animals resulted in neither ARE activation nor neuroprotection. By reintroducing Nrf2 via infection with a replication-deficient adenovirus (ad), both the genetic response and neuroprotection were rescued. Conversely, infection with adenovirus encoding dominant-negative (DN) Nrf2 (ad-DN-Nrf2) or pretreatment with the selective phosphatidylinositol-3 kinase inhibitor LY294002 inhibited the tBHQ-mediated promoter response and corresponding neuroprotection. Interestingly, the adenoviral infection showed a high selectivity for astrocytes over neurons. In an attempt to reveal some of the cell type-specific changes resulting from ARE activation, cultures were
Intracellular Association of Glycine Receptor with Gephyrin Increases Its Plasma Membrane Accumulation Rate

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Gephyrin, a tubulin-binding protein, is the core of inhibitory postsynaptic scaffolds stabilizing glycine receptors (GlyRs) and/or GABAergic B2 receptors. Previous ultrastructural studies in vivo and in vitro have reported a localization of gephyrin to intracellular cisternae during development or after glycineric denervation (Seitanidou et al., 1992; Colin et al., 1996, 1998). These data were compatible with a traffic of this cytoplasmic, but membrane-associated, protein together with membrane proteins such as GlyR after exocytosis and/or endocytosis pathways. We have now investigated the consequences of a GlyR–gephyrin interaction on the localization and the dynamics of these two molecules in African green monkey kidney cells (COS-7) cells and in neurons transfected with green fluorescent protein-tagged-gephyrin and myc-tagged GlyR after exocytosis and/or endocytosis pathways. We have now investigated the consequences of a GlyR–gephyrin interaction on the localization and the dynamics of these two molecules in African green monkey kidney cells (COS-7) cells and in neurons transfected with green fluorescent protein-tagged-gephyrin. Videomicroscopy and nocodazole treatment indicate that the movements of these vesicles are microtubule dependent. Expressing GlyR with a thrombin cleavage site between the myc-tag and the N terminal of the GlyR subunit (Rosenberg et al., 2001) allowed monitoring of newly inserted receptors in the cell surface. Using temperature changes to block GlyR in, and then release it from, the trans-Golgi network, we show that gephyrin accelerates the accumulation of GlyR at the cell surface. Therefore, our data strongly suggest that some GlyR clusters are associated with gephyrin on their way to the cell surface and that this association increases the accumulation of GlyR at the plasma membrane.


The Glutamate Transporter GLT1a Is Expressed in Excitatory Axon Terminals of Mature Hippocampal Neurons

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GLT1 is the major glutamate transporter of the brain and has been thought to be expressed exclusively in astrocytes. Although excitatory axon terminals take up glutamate, the transporter responsible has not been identified. GLT1 is expressed in at least two forms varying in the C termini, GLT1a and GLT1b. GLT1 mRNA has been demonstrated in neurons, without associated protein. Recently, evidence has been presented, using specific C terminus–directed antibodies, that GLT1b protein is expressed in neurons in vivo. These data suggested that the GLT1 mRNA detected in neurons encodes GLT1b and also that GLT1b might be the elusive presynaptic transporter. To test these hypotheses, we used variant-specific probes directed to the 3′-untranslated regions for GLT1a and GLT1b to perform in situ hybridization in the hippocampus. Contrary to expectation, GLT1a mRNA was the more abundant form. To investigate further the expression of GLT1 in neurons in the hippocampus, antibodies raised against the C terminus of GLT1a and against the N terminus of GLT1, found to be specific by testing in GLT1 knock-out mice, were used for light microscopic and EM-ICC. GLT1a protein was detected in neurons, in 14–29% of axons in the hippocampus, depending on the region. Many of the labeled axons formed axo-somatic, asymmetric, and, thus, excitatory synapses. Labeling also occurred in some spines and dendrites. The antibody against the N terminus of GLT1 also produced labeling of neuronal processes. Thus, the originally cloned form of GLT1, GLT1a, is expressed as protein in neurons in the mature hippocampus and may contribute significantly to glutamate uptake into excitatory terminals.


Regulation of Dopamine D1 Receptor Function by Physical Interaction with the NMDA Receptors

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Functional interactions between dopamine D1-like receptors and NMDAergic: A subtype glutamate receptors have been implicated in the maintenance of normal brain activity and neurological dysfunction. Although modulation of NMDA receptor functions by D1 receptor activation has been the subject of extensive investigation, little is known as to how the activation of NMDA receptors alters D1 function. Here we report that NMDA receptors regulate D1 receptor function via a direct protein–protein
interaction mediated by the carboxyl tail regions of both receptors. In both cotransfected cells and cultured hippocampal neurons the activation of NMDA receptors increases the number of D1 receptors on the plasma membrane surface and enhances D1 receptor-mediated cAMP accumulation via a SNARE-dependent mechanism. Furthermore, overexpression of mini-genes encoding either NR1 or D1 carboxyl tail fragments disrupts the D1–NR1 direct protein–protein interaction and abolishes NMDA-induced changes in both D1 cell surface expression and D1-mediated cAMP accumulation. Our results demonstrate that the D1–NR1 physical interaction enables NMDA receptors to increase plasma membrane insertion of D1 receptors and provides a novel mechanism by which the activation of NMDA receptors upregulates D1 receptor function. Understanding the molecular mechanisms by which D1 and NMDA receptors functionally interact may provide insight toward elucidating the molecular neurobiological mechanisms involved in many neuropsychiatric illnesses, such as schizophrenia.


**Olfactory Bulb Glomeruli: External Tufted Cells Intrinsically Burst at Theta Frequency and Are Entrained by Patterned Olfactory Input**

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Glomeruli, the initial sites of synaptic processing in the olfactory system, contain at least three types of neurons collectively referred to as juxtaglomerular (JG) neurons. The role of JG neurons in odor processing is poorly understood. We investigated the morphology, spontaneous, and sensory-evoked activity of one class of JG neurons, external tufted (ET) cells, using whole-cell patch-clamp and extracellular recordings in rat olfactory bulb slices. ET cells have extensive dendrites that ramify within a single glomerulus or, rarely, in two adjacent glomeruli. All ET neurons exhibit spontaneous rhythmic bursts of action potentials (~1–8 bursts/sec). Bursting is intrinsically generated; bursting persisted and became more regular in the presence of ionotropic glutamate and GABA receptor antagonists. Burst frequency is voltage dependent; frequency increased at membrane potentials depolarized relative to rest and decreased during A membrane potential hyperpolarization. Spontaneous bursting persisted in blockers of calcium channels that eliminated low-threshold calcium spikes (LTS) in ET cells. ET cells have a persistent sodium current available at membrane potentials that generate spontaneous bursting. Internal perfusion with a fast sodium channel blocker eliminated A: spontaneous bursting but did not block the LTS. These results suggest that persistent sodium channels are essential for spontaneous burst generation in ET cells. ET cell bursts were entrained to ON stimuli delivered over the range of theta frequencies. Thus, ET cells appear to be tuned to the frequency of sniffing.


**Dopamine and Glutamate Control Area-Restricted Search Behavior in Caenorhabditis elegans**

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Area-restricted search (ARS) is a foraging strategy used by many animals to locate resources. The behavior is characterized by a time-dependent reduction in turning frequency after the last resource encounter. This maximizes the time spent in areas in which resources are abundant and extends the search to a larger area when resources become scarce. We demonstrate that dopaminergic and glutamatergic signaling contribute to the neural circuit controlling ARS in the nematode *Caenorhabditis elegans*. Ablation of dopaminergic neurons eliminated ARS behavior, as did application of the dopamine receptor antagonist raclopride. Furthermore, ARS was affected by mutations in the glutamate receptor subunits GLR1: A-1 and GLR-2 and the EAT-4 glutamate vesicular transporter. Interestingly, preincubation on dopamine restored the behavior in worms with defective dopaminergic signaling, but not in glr-1, glr-2, or eat-4 mutants. This suggests that dopaminergic and glutamatergic signaling function in the same pathway to regulate turn frequency. Both GLR-1 and GLR-2 are expressed in the locomotory control circuit that modulates the direction of locomotion in response to sensory stimuli and the duration of forward movement during foraging. We propose a mechanism for ARS in *C. elegans* in which dopamine, released in response to food, modulates glutamatergic signaling in the locomotory control circuit, thus resulting in an increased turn frequency.


**Ca**\(^{2+}\) Syntillas, Miniature Ca**^{2+}\** Release Events in Terminals of Hypothalamic Neurons, Are Increased in Frequency by Depolarization in the Absence of Ca**^{2+}\** Influx**

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Localized, brief Ca\(^{2+}\) transient (Ca\(^{2+}\) syntillas) caused by release from intracellular stores were found in isolated nerve terminals from magnocellular hypothalamic neurons and examined quantitatively using a signal mass approach to Ca\(^{2+}\) imaging. Ca\(^{2+}\) syntillas (scintilla, L., spark, from a synaptic structure, a nerve terminal) are caused by release of ~250,000 Ca ions on average by a Ca\(^{2+}\) flux lasting on the order of tens of milliseconds and occur spontaneously at a membrane potential of ~80 mV. Syntillas are unaffected by removal of extracellular Ca\(^{2+}\), are mediated by ryanodine receptors (RyRs) and are increased in frequency, in the absence of extracellular Ca\(^{2+}\), by physiological levels of depolarization. This represents the first direct demonstration of mobilization of Ca\(^{2+}\) from intracellular stores in neurons by depolarization without Ca\(^{2+}\) influx. The regulation of syntillas by depolarization provides a new link between neuronal activity and cytosolic Ca\(^{2+}\) in nerve terminals.

KCNQ2 Is a Nodal K⁺ Channel

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Mutations in the gene encoding the K⁺ channel KCNQ2A/Q: C cause neonatal epilepsy and myokymia, indicating that KCNQ2 regulates the excitability of CNS neurons and motor axons, respectively. We show here that KCNQ2 channels are functional components of axon initial segments and nodes of Ranvier, colocalizing with ankyrin-G and voltage-dependent Na⁺ channels throughout the CNS and PNS. Retigabine, which opens KCNQ channels, diminishes axonal excitability. Linopirdine, which blocks KCNQ channels, prolongs the repolarization of the action potential in neonatal nerves. The clustering of KCNQ2 at nodes and initial segments lags that of ankyrin-G during development, and both ankyrin-G and KCNQ2 can be coimmunoprecipitated in the brain. KCNQ3 is also a component of some initial segments and nodes in the brain. The diminished activity of mutant KCNQ2 channels accounts for neonatal epilepsy and myokymia; the cellular locus of these effects may be axonal initial segments and nodes.

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DEVELOPMENT/PLASTICITY/REPAIR

Ephrin-A5 Exerts Positive or Inhibitory Effects on Distinct Subsets of EphA4-Positive Motor Neurons

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Eph receptor tyrosine kinases and ephrins are required for axon patterning and plasticity in the developing nervous system. Typically, Eph–ephrin interactions promote inhibitory events; for example, prohibiting the entry of neural cells into certain embryonic territories. Here, we show that distinct subsets of motor neurons that express EphA4 respond differently to ephrin-A5. EphA4-positive LMC(l) axons avoid entering ephrin-A5-positive hindlimb mesoderm. In contrast, EphA4-positive MMC(m) axons extend through ephrin-A5-positive rostral half-sclerotome. Blocking EphA4 activation in MMC(m) neurons or expanding the domain of ephrin-A5 expression in the somite results in the aberrant growth of MMC(m) axons into the caudal half-sclerotome. Moreover, premature expression of EphA4 in MMC(m) neurons leads to a portion of their axons growing into novel ephrin-A5-positive territories. Together, these results indicate that EphA4-ephrin-A5 signaling acts in a positive manner to constrain MMC(m) axons to the rostral half-sclerotome. Furthermore, we show that Eph activation localizes to distinct subcellular compartments of LMC(l) and MMC(m) neurons, consistent with distinct EphA4 signaling cascades in these neuronal subpopulations.


A Novel cAMP-Dependent Pathway Activates Neuronal Integrin Function in Retinal Neurons

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Retinal neurons lose the ability to attach to and extend neurites on substrata of laminin-1 (LN-1) during late embryogenesis, in a time frame that corresponds to target innervation. Although this developmental loss correlates with a modest downregulation of integrin expression, we have shown previously that these neurons use the same laminin-binding integrins for outgrowth on other laminin isoforms to which responsivity has not been lost (Ivins et al., 1998), suggesting that integrin functional states may be a critical point of regulation. Consistent with this view, expression of an activated mutant of R-ras, an activator of integrin function, restores integrin-dependent outgrowth of late embryonic retinal neurons on LN-1 (Ivins et al., 2000). Because cyclic nucleotides have been implicated in the regulation of integrin function in non-neuronal cells, as well as in the regulation of growth cone responses to various axon growth inhibitors, we asked whether raising cAMP levels in late embryonic retinal neurons could activate neuronal integrin function and restore neurite outgrowth on LN-1. We find that, similar to R-ras expression, raising cAMP levels in these neurons promotes β6/β1 integrin-dependent neurite outgrowth. Surprisingly, these effects of cAMP are independent of protein kinase A and cAMP/Rap pathway and suggest the existence of a novel cAMP-dependent mechanism.

Through the recording electrode. Administration of a D1 antagonist (SCH 23390; AQ: C 0.5 mg/kg, i.p.) had no effect on the VTA reduction of PFC-elicited responses, whereas spontaneously occurring up states. Furthermore, no attenuation of PFC-elicited responses was observed during depolarization produced by positive current injection. Membrane depolarization alone, because EPSPs evoked during the sustained depolarization after VTA stimulation were significantly smaller than EPSPs evoked during mimicking dopamine cell burst firing. PFC-elicited EPSPs were smaller in amplitude and faster to decay after VTA stimulation. These changes could not be explained by administration of a D2 antagonist (eticlopride; 0.5 mg/kg, i.p.) reversed the reduction of PFC inputs when the analysis was limited to comparisons with spontaneous up states. These results suggest that the ability of PFC inputs to drive accumbens neurons is dampened by dopamine acting primarily at D2 receptors. Along with previous reports of dopaminergic attenuation of limbic afferents to the accumbens, these findings support the hypothesis that dopamine mediates the selection and integration of excitatory inputs and thus shapes information processing in accumbens output neurons.

**BEHAVIORAL/SYSTEMS/COGNITIVE**

### A New Rat Model of the Human Serial Reaction Time Task: Contrasting Effects of Caudate and Hippocampal Lesions

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There is often little correspondence between human and animal examples of nondeclarative memory. The serial reaction time task (SRT) is a sequence learning example of human nondeclarative memory that may be suitable for development as an animal model. The SRT is believed to be impaired by basal ganglia, not limbic system damage, but there is uncertainty whether limbic system pathology does in fact leave the SRT unimpaired. We therefore developed a new rat model that closely approximated the human SRT, using intracranial self-stimulation to promote rapid continuous responding to four adjacent nose pokes in a single test session. Intact rats that experienced repeated sequences demonstrated robust interference effects when switched to a random sequence of cued responses (at 4-, 8-, and 12-sequence lengths), unlike intact controls that experienced the random sequences only. The interference effect in the human task is a key measure for nondeclarative sequence learning. Rats with dorsal caudate lesions that experienced massed sequence repetitions showed an interference effect at the four-sequence length only. By contrast, rats with dorsal hippocampal lesions showed an interference effect at all sequence lengths. This new rat SRT model clarifies the basal ganglia–limbic system dichotomy suggested by human work.


### Dopaminergic Modulation of Prefrontal Cortical Input to Nucleus Accumbens Neurons *In Vivo*

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Dopaminergic transmission in the nucleus accumbens has been proposed to modulate the effects of converging excitatory inputs from the cortex, hippocampus, and amygdala. Here, we used *in vivo* intracellular recording in anesthetized rats to examine the response of nucleus accumbens neurons to stimulation of the prefrontal cortex (PFC). A and the ventral tegmental area (VTA). The EPSP elicited in accumbens neurons by PFC stimulation was attenuated by VTA train stimulation in a pattern mimicking dopamine cell burst firing. PFC-elicted EPSPs were smaller in amplitude and faster to decay after VTA stimulation. These changes could not be explained by membrane depolarization alone, because EPSPs evoked during the sustained depolarization after VTA stimulation were significantly smaller than EPSPs evoked during spontaneously occurring up states. A: B Furthermore, no attenuation of PFC-elicted responses was observed during depolarization produced by positive current injection through the recording electrode. Administration of a D1 antagonist (SCH 23390; AQ: C 0.5 mg/kg, i.p.) had no effect on the VTA reduction of PFC inputs when the analysis was limited to comparisons with spontaneous up states. These results suggest that the ability of PFC inputs to drive accumbens neurons is dampened by dopamine acting primarily at D2 receptors. Along with previous reports of dopaminergic attenuation of limbic afferents to the accumbens, these findings support the hypothesis that dopamine mediates the selection and integration of excitatory inputs and thus shapes information processing in accumbens output neurons.

Intracranial Self-Administration of Ethanol within the Ventral Tegmental Area of Male Wistar Rats: Evidence for Involvement of Dopamine Neurons

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Previous work from our laboratory indicated that female Wistar rats will self-administer ethanol (EtOH) directly into the posterior ventral tegmental area (VTA). These results suggested that VTA dopamine (DA) neurons might be involved in mediating the reinforcing actions of EtOH within this region. The objectives of this study were to determine (1) the dose–response effects for the self-administration of EtOH into the VTA of male Wistar rats, and (2) the involvement of VTA DA neurons in the reinforcing actions of EtOH within the VTA. Adult male Wistar rats were implanted stereotaxically with guide cannulas: A aimed at the posterior or anterior VTA. After 1 week, rats were placed in standard two-lever (active and inactive) experimental chambers for a total of seven to eight sessions. The first experiment determined the intracranial self-administration of EtOH (0–400 mg% A: B) into the posterior and anterior VTA. The second experiment examined the effects of coadministration of the D2 agonist quinpirole on the acquisition and maintenance of EtOH self-infusions into the posterior VTA. The final experiment determined the effects of a D2 antagonist (sulpride) to reinstate self-administration behavior in rats given EtOH and quinpirole to coadminister. Male Wistar rats self-infused 100–300 mg% EtOH directly into the posterior, but not anterior, VTA. Coadministration of quinpirole prevented the acquisition and extinguished the maintenance of EtOH self-infusion into the posterior VTA, and addition of sulpride reinstated EtOH self-administration. The results of this study indicate that EtOH is reinforcing within the posterior VTA of male Wistar rats and suggest that activation of VTA DA neurons is involved in this process.

Ventral Pallidal Representation of Pavlovian Cues and Reward: Population and Rate Codes

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We recorded neural activity in the ventral pallidum (VP) while rats learned a pavlovian reward association. Rats learned to distinguish a tone that predicted sucrose pellets (CS+) from a different tone that predicted nothing (CS−). Many VP units became responsive to CS+, but few units responded to CS−. When two CS+ were encountered sequentially, the earliest predictor of reward became most potent. Many VP units were also activated when the sucrose reward was received [unconditioned stimulus (UCS)]. These VP units for UCS remained responsive to sucrose reward after learning, even when sucrose was already predicted by CS+. Neural representation of reward learning and reward itself was characterized by population codes. The population of units that responded to CS+ increased with learning, whereas the population that responded to UCS did not change. A relative firing rate code also represented the identities of conditioned stimuli: A and UCS. Firing rate differences among stimuli were acquired early and remained stable during subsequent training, whereas population codes and behavioral conditioned responses continued to develop during subsequent training. Thus, the VP makes use of dynamic CS population and rate codes to encode pavlovian reward cues in reward learning and uses stable UCS population and firing codes to encode sucrose reward itself.

L and M Cone Contributions to the Midget and Parasol Ganglion Cell Receptive Fields of Macaque Monkey Retina

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Analysis of cone inputs to primate parvocellular ganglion cells suggests that red–green spectral opponency results when connections segregate input from long wavelength (L) or middle wavelength (M) sensitive cones to receptive field centers and surrounds. However, selective circuitry is not an obvious retinal feature. Rather, cone receptive field surrounds and H1 horizontal cells get mixed L and M cone input, likely indiscriminately sampled from the randomly arranged cones of the photoreceptor mosaic. Red–green spectral opponency is consistent with random connections in central retina where the mixed cone ganglion cell surround is opposed by a single cone input to the receptive field center, but not in peripheral retina where centers get multiple cone inputs. The selective and random connection hypotheses might be reconciled if cone type selective circuitry existed in inner retina. If so, the segregation of L and M cone inputs to receptive field centers and surrounds would increase from horizontal to ganglion cell, and opponency would remain strong in peripheral retina. We measured the relative strengths of L and M cone inputs to H1 horizontal cells and parasol and midget ganglion cells by recording intracellular physiological responses from morphologically identified neurons in an in vitro preparation of the macaque monkey retina. The relative strength of L and M cone inputs to H1 and ganglion cells at the same locations matched closely. Peripheral midget cells were nonopponent. These results suggest that peripheral H1 and ganglion cells inherit their L and M cone inputs from the photoreceptor mosaic unmodified by selective circuitry.
Differential Responses in Human Striatum and Prefrontal Cortex to Changes in Object and Rule Relevance

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Event-related functional magnetic resonance imaging was used to measure blood oxygenation level-dependent responses in 16 young healthy human volunteers during performance of an attentional switching task. The task allowed the separate investigation of lower-order switching between concrete objects and higher-order switching between abstract task rules. Significant signal change in the ventral striatum was demonstrated on trials when subjects switched between objects but not when subjects switched between abstract task rules. In contrast, signal change in the lateral prefrontal cortex (PFC) was observed during all switch trials. The switch-related responses were not contaminated by task difficulty, because the greatest signal change was observed during the relatively easy switch trials, which required both lower-order and higher-order switching at the same time. The present data suggest that mechanisms of inhibitory response control in frontostriatal systems are organized according to distinct levels of abstraction. Specifically, the response selection computation carried by the ventral striatum, which projects to the orbitofrontal cortex and the medial PFC, is restricted to the transformation of concrete stimulus exemplar information into motor responses, whereas the adaptive function of the lateral PFC extends to the transformation of abstract task-rule representations into action.


Fast Remapping of Sensory Stimuli onto Motor Actions on the Basis of Contextual Modulation

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Higher organisms can establish complex associations between sensory events and motor responses. More remarkable than their complexity, however, is that the resulting sensory-motor maps can be selectively interchanged. For example, a person who speaks English and Spanish can read aloud “con once, sin once,” going effortlessly from one language to the other. What is the neural basis of this capacity? Here, a network model is presented in which multiple maps between sensory stimuli and motor actions are possible, but only one of them, depending on behavioral context, is implemented at any given time. The key is a nonlinear representation in which the gain of sensory responses is regulated by context information. Neuronal responses can indeed show variations in gain, as has been documented in the case of proprioceptive signals such as eye and head position, which can modulate visually triggered activity. However, in contrast to these, the contextual cues used here need not bear any relationship to the physical attributes of the stimuli; in particular, spatial location is irrelevant. The model thus posits the existence of sensory neurons that are nonlinearly modulated by arbitrary context signals, a plausible and testable prediction. The proposed mechanism allows a network of neurons to effectively change the functional connectivity between its inputs and outputs and may partially explain how animals can quickly adapt their behavior to varying environmental conditions.

The Journal of Neuroscience, February 4, 2004 • 24(5):1089 –1100

Linearity of Cortical Receptive Fields Measured with Natural Sounds

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How do cortical neurons represent the acoustic environment? This question is often addressed by probing with simple stimuli such as clicks or tone pips. Such stimuli have the advantage of yielding easily interpreted answers, but have the disadvantage that they may fail to uncover complex or higher-order neuronal response properties. Here, we adopt an alternative approach, probing neuronal responses with complex acoustic stimuli, including animal vocalizations. We used in vivo whole-cell methods in the rat auditory cortex to record subthreshold membrane potential fluctuations elicited by these stimuli. Most neurons responded robustly and reliably to the complex stimuli in our ensemble. Using regularization techniques, we estimated the linear component, the spectrottemporal receptive field (STRF), of the transformation from the sound (as represented by its time-varying spectrogram) to the membrane potential of the neuron. A. We find that the STRF has a rich dynamical structure, including excitatory regions positioned in general accord with the prediction of the classical tuning curve. However, whereas the STRF successfully predicts the responses to some of the natural stimuli, it surprisingly fails completely to predict the responses to others; on average, only 11% of the response power could be predicted by the STRF. Therefore, most of the response of the neuron cannot be predicted by the linear component, although the response is deterministically related to the stimulus. Analysis of the systematic errors of the STRF model shows that this failure cannot be attributed to simple nonlinearities such as adaptation to mean intensity, rectification, or saturation. Rather, the highly nonlinear response properties of auditory cortical neurons must be attributable to: B nonlinear interactions between sound frequencies and time-varying properties of the neural encoder.

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Dynamics of Precise Spike Timing in Primary Auditory Cortex

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Although single units in primary auditory cortex (A1) exhibit accurate timing in their phasic response to the onset of sound (precision of a few milliseconds), paradoxically, they are unable to sustain synchronized responses to repeated stimuli at rates much beyond 20 Hz. To explore the relationship between these two aspects of cortical response, we designed a broadband stimulus with a slowly modulated spectrotemporal envelope riding on top of a rapidly modulated waveform (or fine structure). Using this stimulus, we quantified the ability of cortical cells to encode independently and simultaneously: A) the stimulus envelope and fine structure. Specifically, by reverse-correlating unit responses with these two stimulus dimensions, we measured the spectrotemporal response fields (STRFs) associated with the processing of the envelope, the fine structure, and the complete stimulus. A1 cells respond well to the slow spectrotemporal envelopes and produce a wide variety of STRFs. In over 70% of cases, A1 units also track the fine-structure modulations precisely, throughout the stimulus, and for frequencies up to several hundred Hertz. Such a dual response, however, is contingent on the cell being driven by both fast and slow modulations, in that the response to the slowly modulated envelope gates the expression of the fine structure. We also demonstrate that either a simplified model of synaptic depression and facilitation, and/or a cortical network of thalamic excitation and cortical inhibition can account for major trends in the observed findings. Finally, we discuss the potential functional significance and perceptual relevance of these coexistent, complementary dynamic response modes.

Functional Magnetic Resonance Imaging Examination of Two Modular Architectures for Switching Multiple Internal Models

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An internal model is a neural mechanism that can mimic the input→output properties of a controlled object such as a tool. Recent research interests have moved on to how multiple internal models are learned and switched under a given context of behavior. Two representative computational models for task switching propose distinct neural mechanisms, thus predicting different brain activity patterns in the switching of internal models. In one model, called the mixture-of-experts architecture, switching is commanded by a single executive called a “gating network,” which is different from the internal models. In the other model, called the MOSAIC (Modular Selection And Identification for Control), the internal models themselves play crucial roles in switching. Consequently, the mixture-of-experts model predicts that neural activities related to switching and internal models can be temporally and spatially segregated, whereas the MOSAIC model predicts that they are closely intermingled. Here, we directly examined the two predictions by analyzing functional magnetic resonance imaging activities during the switching of one common tool (an ordinary computer mouse) and two novel tools: a rotated mouse, the cursor of which appears in a rotated position, and a velocity mouse, the cursor velocity of which is proportional to the mouse position. The switching and internal model activities temporally and spatially overlapped each other in the cerebellum and in the parietal cortex, whereas the overlap was very small in the frontal cortex. These results suggest that switching mechanisms in the frontal cortex can be explained by the mixture-of-experts architecture, whereas those in the cerebellum and the parietal cortex are explained by the MOSAIC model.

Unique Neural Circuitry for Neonatal Olfactory Learning

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Imprinting ensures that the infant forms the caregiver attachment necessary for altricial species survival. In our mammalian model of imprinting, neonatal rats rapidly learn the odor-based maternal attachment. This rapid learning requires reward-evoked locus ceruleus (LC) release of copious amounts of norepinephrine (NE) into the olfactory bulb. This imprinting ends at postnatal day 10 (P10); A: B and is associated with a dramatic reduction in reward-evoked LC NE release. Here we assess whether the functional emergence of LC α1α1 agonists C2 inhibitory autoreceptors and the downregulation of LC α1 excitatory autoreceptors underlie the dramatic reduction in NE release associated with termination of the sensitive period. Postautoreceptor period pups (P12) were implanted with either LC or olfactory bulb cannulas, classically conditioned with intracranial drug infusions (P14), and tested for an odor preference (P15). During conditioning, a novel odor was paired with either olfactory bulb infusion of a β-receptor agonist (isoproterenol) to assess the target effects of NE or direct LC cholinergic stimulation combined with α2 antagonists and α1 agonists in a mixture to reinstate neonatal levels of LC autoreceptor activity to assess the source of NE. Pups learned an odor preference when the odor was paired with either olfactory bulb isoproterenol infusion or reinstatement of neonatal LC receptor activity. These results suggest that LC autoreceptor functional changes rather than olfactory bulb changes underlie sensitive period termination.
Macaque Ventral Premotor Cortex Exerts Powerful Facilitation of Motor Cortex Outputs to Upper Limb Motoneurons

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The ventral premotor area (F5) is part of the cortical circuit controlling visuomotor grasp. F5 could influence hand motor function through at least two pathways: corticospinal projections and corticocortical projections to primary motor cortex (M1). We found that stimulation of macaque F5, which by itself evoked little or no detectable corticospinal output, could produce a robust modulation of motor outputs from M1. Arrays of fine microwires were implanted in F5 and M1. During terminal experiments under chloralose anesthesia, single stimuli delivered to M1 electrodes evoked direct (D) and indirect (I1, I2, and I3) corticospinal volleys. In contrast, single F5 shocks were ineffective; double shocks (3 msec separation) evoked small I waves but no D wave. However, when the test (T) M1 shock was conditioned (C) by single or double F5 shocks, there was strong facilitation of I1 and I2 waves from M1, with C–T intervals of <1 msec. Intracellular recordings from 79 arm and hand motoneurons (MNs) revealed no postsynaptic effects from single F5 shocks. In contrast, these stimuli produced a robust facilitation of I2 and I3 EPSPs evoked from M1 (60% of MNs); this was particularly marked in hand muscle MNs (92%). Muscimol injection in M1 reduced I waves from F5 and abolished the F5-induced facilitation of late I waves from M1, and of EPSPs associated with them. Thus, some motor effects evoked from F5 may be mediated by corticocortical inputs to M1 impinging on interneurons generating late corticospinal I waves. Similar mechanisms may allow F5 to modulate grasp-related outputs from M1.


NEUROBIOLOGY OF DISEASE

Acid-Sensing Ion Channel 2 Is Important for Retinal Function and Protects against Light-Induced Retinal Degeneration

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pH variations in the retina are thought to be involved in the fine-tuning of visual perception. We show that both photoreceptors and neurons of the mouse retina express the H+-gated cation channel subunits acid-sensing ion channel 2a (ASIC2a) and ASIC2b. Inactivation of the ASIC2 gene in mice leads to an increase in the rod electroretinogram a- and b-waves and thus to an enhanced gain of visual transduction. ASIC2 knock-out mice are also more sensitive to light-induced retinal degeneration. We suggest that ASIC2 is a negative modulator of rod phototransduction, and that functional ASIC2 channels are beneficial for the maintenance of retinal integrity.

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NEUROBIOLOGY OF DISEASE

Efficacy of Rehabilitative Experience Declines with Time after Focal Ischemic Brain Injury

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To maximize the effectiveness of rehabilitative therapies after stroke, it is critical to determine when the brain is most responsive (i.e., plastic) to sensorimotor experience after injury and to focus such efforts within this period. Here, we compared the efficacy of 5 weeks of enriched rehabilitation (ER) initiated at 5 d (ER5), ER14, or ER30 after focal ischemia, as judged by functional outcome and neuromorphological change. ER5 provided marked improvement in skilled forelimb reaching ability and ladder-rung- and narrow-beam-walking tasks and attenuated the stroke-induced reliance on the unaffected forepaw for postural support. ER14 provided improvement to a somewhat lesser extent, whereas recovery was diminished after ER30 such that motor function did not differ from ischemic animals exposed to social housing.

To examine potential neural substrates of the improved function, we examined dendritic morphology in the undamaged motor cortex because our previous work (Biernaskie and Corbett, 2001) suggested that recovery was associated with enhanced dendritic growth in this region. ER5 increased the number of branches and complexity of layer V neurons compared with both social housing and control animals. Dendritic arbor after ER14 (although increased) and ER30 did not differ from those exposed to social housing. These data suggest that the poststroke brain displays heightened sensitivity to rehabilitative experience early after the stroke but declines with time. These findings have important implications for rehabilitation of stroke patients, many of whom experience considerable delays before therapy is initiated.

The Journal of Neuroscience, February 4, 2004 • 24(5):1245–1254
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