This Week in The Journal

● Cellular/Molecular

A Cool Receptor in the Spinal Cord?

Kenzo Tsuzuki, Hong Xing, Jennifer Ling, and Jianguo G. Gu
(see pages 762–771)

The recently cloned cold- and menthol-sensitive receptor, TRPM8, is a member of the large and diverse transient receptor potential (TRP) family. This nonselective cation channel is permeable to calcium and is expressed in some primary afferent neurons. One might expect that the cold receptor would be expressed primarily on peripheral nerve endings. However Tsuzuki et al. report a possible central action of the cold receptor. They examined synapses in cocultured DRG and dorsal horn (DH) neurons. Both cooling and menthol application increased the frequency of miniature EPSCs without affecting the amplitude. Menthol also enhanced evoked release from DRG neurons, consistent with a presynaptic site of action. These actions appeared to depend on intracellular calcium stores but not on extracellular calcium or conventional intracellular signaling pathways. Thus the authors propose that the cold receptor is expressed on intracellular membranes causing direct release of calcium stores.

▲ Development/Plasticity/Repair

Maternal Separation, Fear, and the Amygdala

M. D. Bauman, P. Lavenex, W. A. Mason, J. P. Capitanio, and D. G. Amaral
(see pages 711–721)

The amygdala has a well accepted role in fear-related behaviors. However its role in social interactions is not as clear. Bauman et al. test the relationship of fear and social interactions in an interesting situation: the relationship between mother and infant. They studied infant macaque monkeys after bilateral lesions of the amygdala or hippocampus. Amygdala-lesioned monkeys had increased physical contact time with their mothers, but otherwise showed normal maternal interactions. However after weaning at 6 months, amygdala-lesioned monkeys did not seek out their mothers or display distress signals in a "maternal preference test." This test seemingly measures the equivalent of separation anxiety familiar to human moms. The authors attribute the disrupted behavior as an impaired ability to perceive danger. The results suggest that the amygdala is not essential for the development of social behavior; rather, it mediates responses to dangerous or fear-provoking situations.

■ Behavioral/Systems/Cognitive

Nociceptive Inputs to Rat Cortex

Caroline Gauriau and Jean-François Bernard
(see pages 752–761)

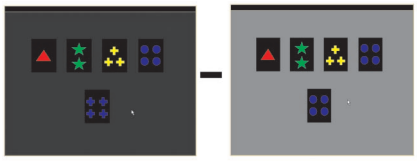
The thalamic and cortical pain-processing areas are not as well mapped as in other sensory systems. Several cortical areas are activated by pain, but their thalamic connections are still in question. In this issue, Gauriau and Bernard take a look at the posterior triangular thalamus (PoT) as a potential relay between nociceptive sensory neurons in lamina 1 of the spinal cord and the cortex. The authors recorded the sensory modalities of rat PoT neurons using extracellular recording. Approximately one-half of the neurons responded to tactile or nociceptive stimulation. Of these, one-half were nociceptive-specific (NS), whereas the other half responded to both stimuli [nociceptive nonspecific (NNS)] or only to tactile stimuli. The cells were then labeled with biotin–dextran to map their cortical projections. Interestingly, the pain-processing neurons innervated different sites according to their sensory fingerprint. NNS and tactile-responsive neurons projected primarily to the insular cortex and amygdala, whereas NS neurons terminated exclusively in somatosensory cortex S2. The results suggest distinct cortical components in pain processing.

◆ Neurobiology of Disease

Probing Cognitive Deficits in Parkinson's Disease

Oury Monchi, Michael Petrides, Julien Doyon, Ronald B. Postuma, Keith Worsley, and Alain Dagher
(see pages 702–710)

Among the cognitive deficits that accompany Parkinson's disease (PD) are difficulties in "set shifting," or adjusting one's behavior to match changing circumstances. This deficit can be viewed as a slowing of mental processes analogous to the slow initiation of movement (bradykinesia) that is one of the hallmarks of PD. Similar set-shifting problems also occur in patients with lesions of the prefrontal cortex (PFC), as detected by the Wisconsin Card Sorting Task (WCST). This task requires subjects to sort objects according to constantly changing criteria. In this week's *Journal*, Monchi et al. used functional magnetic resonance imaging to examine PFC activity during the set-shifting task. Negative feedback or matching after negative feedback on the WCST caused coactivation of the striatum and specific regions of the PFC. This localized PFC activation was decreased in PD, suggesting that depletion of nigrostriatal dopamine may be responsible for the set-shifting deficit. Other subregions of the PFC actually showed increased activity during WCST in PD subjects, which the authors attribute to decreases in intracortical dopamine.



In the WCST, the subject is asked to match test cards (bottom) to reference cards (4 top cards) according to one of three rules (color, number, shape). An unannounced change in the classification requires set shifting. See the article by Monchi et al. for details.

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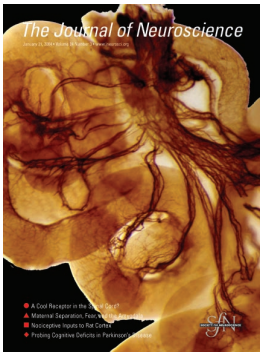
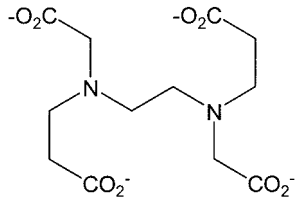
January 21, 2004 • Volume 24 Number 3 www.jneurosci.org



Cover picture: Proper development of sympathetic innervation of the gastrointestinal tract is critical for its function. Whole-mount tyrosine hydroxylase immunostaining of the mouse gastrointestinal tract reveals the extent of perinatal sympathetic innervation, with sympathetic axons traveling along mesenteric arterial vasculature supplying blood to the intestines. NGF plays a crucial role in the development of this intricate pattern of sympathetic target innervation independently of its requirement for neuron survival. For details, see the article by Glebova and Ginty in this issue (pages 743–751).



Also, the first sentence on page 6852 should begin "If the value of f_{max}/f_{min} is ...."

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Brief Communications

Reduced Serotonin Type 1_A Receptor Binding in Panic Disorder

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Recent animal models suggest that disturbances in serotonin type-1A receptor (5-HT_{1A}R) function may contribute to chronic anxiety, although it is not clear at all whether such models constitute relevant models for panic disorder (PD) in humans. The selective 5-HT_{1A}R radioligand [18F]trans-4-fluoro-*N*-2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-*N*-(2-pyridyl)cyclohexanecarboxamide (FCWAY) permits *in vivo* assessment of central 5-HT_{1A}R binding using positron emission tomography (PET). We studied 16 unmedicated symptomatic outpatients with PD and 15 matched healthy controls. Seven patients had an additional diagnosis of a current major depressive episode, however PD was the primary diagnosis. A 120 min PET study of 5-HT_{1A}R binding was acquired using a GE Advance scanner in three-dimensional mode. Using quantitative PET image analysis, regional values were obtained for [18F]-FCWAY volume of distribution (DV), corrected for plasma protein binding, and K1, the delivery rate of [18F]-FCWAY from plasma to tissue. MRI scanning was performed using a GE Signa Scanner (3.0 Tesla) to provide an anatomical framework for image analysis and partial volume correction of PET data. PD patients showed lower DV in the anterior cingulate ($t = 4.3$; $p < 0.001$), posterior cingulate ($t = 4.1$; $p < 0.001$), and raphe ($t = 3.1$; $p = 0.004$). Comparing patients with PD, patients with PD and comorbid depression, and healthy controls revealed that DVs did not differ between PD patients and PD patients with comorbid depression, whereas both patient groups differed significantly from controls. These results provide for the first time *in vivo* evidence for the involvement of 5-HT_{1A}Rs in the pathophysiology of PD.

The Journal of Neuroscience, January 21, 2004 • 24(3):589–591

M Channels Containing KCNQ2 Subunits Modulate Norepinephrine, Aspartate, and GABA Release from Hippocampal Nerve Terminals

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KCNQ subunits encode for the M current (I_{KM}), a neuron-specific voltage-dependent K^+ current with a well established role in the control of neuronal excitability. In this study, by means of a combined biochemical, pharmacological, and electrophysiological approach, the role of presynaptic I_{KM} in the release of previously taken up tritiated norepineprine (NE), GABAAQ: C, and D-aspartate (D-ASP) from hippocampal nerve terminals (synaptosomes) has been evaluated. Retigabine (RT) (0.01–30 μM), a specific activator of I_{KM}, inhibited [^{3}H]NE, [^{3}H]D-ASP, and [^{3}H]GABA release evoked by 9 mM extracellular K^+ ($[K^+]_e$). RT-induced inhibition of [^{3}H]NE release was prevented by synaptosomal entrapment of polyclonal antibodies directed against KCNQ2 subunits, an effect that was abolished by antibody preabsorption with the KCNQ2 immunizing peptide; antibodies against KCNQ3 subunits were ineffective. Flupirtine (FP), a structural analog of RT, also inhibited 9 mM $[K^+]_e$-induced [^{3}H]NE release, although its maximal inhibitionAQ: D was lower than that of RT. Electrophysiological studies in KCNQ2-transfected Chinese hamster ovary cells revealed that RT and FP (10 μM) caused a -19 and -9 mV hyperpolarizing shift, respectively, in the voltage dependence of activation of KCNQ2 K^+ channels. In the same cells, the cognition enhancer 10,10-bis(4-pyridinylmethyl)-9(10H)-anthracenone (XE-991) (10 μM) blocked KCNQ2 channels and prevented their activation by RT (1–10 μM). Finally, both XE-991 (10–100 μM) and tetraethylammonium ions (100 μM) abolished the inhibitory effect of RT (1 μM) on [^{3}H]NE release. These findings provide novel evidence for a major regulatory role of KCNQ2 K^+ channel subunits in neurotransmitter release from rat hippocampal nerve endings.

The Journal of Neuroscience, January 21, 2004 • 24(3):592–597

The Suprachiasmatic Nucleus Entrains, But Does Not Sustain, Circadian Rhythmicity in the Olfactory Bulb

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The suprachiasmatic nucleus (SCN) of the hypothalamus has been termed the master circadian pacemaker of mammals. Recent discoveries of damped circadian oscillators in other tissues have led to the hypothesis that the SCN synchronizes and sustains daily rhythms in these tissues. We studied the effects of constant lighting (LL) and of SCN lesions on behavioral rhythmicity and *Period 1* (*Per1*) gene activity in the SCN and olfactory bulb (OB). We found that LL had similar effects on cyclic locomotor and feeding behaviors and *Per1* expression in the SCN but had no effect on rhythmic *Period 1* expression in the OB. LL lengthened the period of locomotor and SCN rhythms by ~1.6 hr. After 2 weeks in LL, nearly 35% of rats lost behavioral rhythmicity. Of these, 90% showed no rhythm in *Per1*-driven expression in their SCN. Returning the animals to constant darkness rapidly restored their daily cycles of running wheel activity and gene expression in the SCN. In contrast, the OB remained rhythmic with no significant change in period, even when cultured from animals that had been behaviorally arrhythmic for 1 month. Similarly, we found that lesions of the SCN abolished circadian rhythms in behavior but not in the OB. Together, these results suggest that LL causes the SCN to lose circadian rhythmicity and its ability to coordinate daily locomotor and feeding rhythms. The SCN, however, is not required to sustain all rhythms because the OB continues to oscillate *in vivo* when the SCN is arrhythmic or ablated.

The Journal of Neuroscience, January 21, 2004 • 24(3):615–619

Articles

CELLULAR/MOLECULAR

Distance-Dependent Scaling of Calcium Transients Evoked by Backpropagating Spikes and Synaptic Activity in Dendrites of Hippocampal Interneurons

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Although interactions between backpropagating action potentials and synaptic stimulations have been extensively studied in pyramidal neurons, dendritic propagation and the summation of these signals in interneurons are not nearly as well known. In this study, two-photon imaging was used to explore the basic properties of dendritic calcium signaling in CA1 stratum radiatum interneurons. In contrast to hippocampal pyramidal neurons, the backpropagating action potential-evoked calcium transients in dendrites of interneurons underwent a distance-dependent increment. Although, in proximal dendrites, an increment could be attributed to a smaller dendrite diameter, distal dendrites did not show such dependence. Calcium responses in interneurons had a smaller amplitude, slower rise time, and decay than in pyramidal neurons. To explore the factors underlying the difference, we compared the calcium-binding capacity in interneurons and in pyramidal neurons. Our finding that endogenous calcium buffers had a higher level in interneurons may primarily explain the different kinetics and amplitudes of calcium transients. Synaptic stimulation-evoked calcium transients were also larger at distant dendritic locations. The spread of these signals was restricted to 12–13 μm long dendritic compartments. Supporting the reported lack of long-term potentiation in these interneurons, we found only sublinear or linear summations of calcium responses to coincident synaptic inputs and backpropagating spikes.

The Journal of Neuroscience, January 21, 2004 • 24(3):661–670

A C-Terminal Determinant of GluR6 Kainate Receptor Trafficking

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Intracellular trafficking of ionotropic glutamate receptors is regulated predominantly by determinants in the cytoplasmic C-terminal domain of the subunit proteins. Although AMPA receptors are found at the vast majority of excitatory synapses, synaptic kainate receptors exhibit a much more restricted distribution, suggesting that specific mechanisms exist for selective trafficking of these receptor proteins. In this report, we define a critical forward trafficking motif that is necessary for surface expression of the glutamate receptor 6 (GluR6)AQ: C kainate receptor as well as chimeric proteins containing only the GluR6 C-terminal domain. The trafficking determinant was identified by tracking surface expression of green fluorescent protein-tagged GluR6 receptors with confocal immunofluorescence in COS-7AQ: D cells and cultured neurons and patch-clamp electrophysiology in human embryonic kidney 293 cells. Serial truncation and alanine site mutagenesis of the GluR6 subunit C terminus localized the critical motif to a seven amino acid stretch of predominantly basic residues. Alanine mutation of the trafficking motif reduced kainate receptor current amplitudes by >90% and resulted in retention of the mutated receptors in the endoplasmic reticulum. This forward trafficking domain is the first such identified for kainate receptors.

The Journal of Neuroscience, January 21, 2004 • 24(3):679–691

Intracellular Astrocyte Calcium Waves *In Situ* Increase the Frequency of Spontaneous AMPA Receptor Currents in CA1 Pyramidal Neurons

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Spontaneous neurotransmitter release and activation of group I metabotropic glutamate receptors (mGluRs) each play a role in the plasticity of neuronal synapses. Astrocytes may contribute to short- and long-term synaptic changes by signaling to neurons via these processes. Spontaneous whole-cell AMPA receptor (AMPAR) currents were recorded in CA1 pyramidal cells *in situ* while evoking Ca^{2+} increases in the adjacent stratum radiatum astrocytes by uncaging IP_3. Whole-cell patch clamp was used to deliver caged IP_3 and the Ca^{2+} indicator dye Oregon green BAPTA-1 to astrocytes. Neurons were patch-clamped and filled with Alexa 568 hydrazide dye to visualize their morphological relationship to the astrocyte. On uncaging of IP_3, astrocyte Ca^{2+} responses reliably propagated as a wave into the very fine distal processes, synchronizing Ca^{2+} activity within astrocyte microdomains. The intracellular astrocyte Ca^{2+} wave coincided with a significant increase in the frequency of AMPA spontaneous EPSCs, but with no change in their kinetics. AMPAR current amplitudes were increased as well, but not significantly ($p = 0.06$). The increased frequency of AMPAR currents was sensitive to the group I mGluR antagonists LY367385 and 2-methyl-6-(phenylethynyl)-pyridineAQ: A, suggesting that (1) astrocytes released glutamate in response to IP_3 uncaging, and (2) glutamate released by astrocytes activated group I mGluRs to facilitate the release of glutamate from excitatory neuronal presynaptic boutons. These results extend previous studies, which have shown astrocyte modulation of neuronal activity *in vitro* and suggest that astrocyte-to-neuron signaling in intact tissue may contribute to synaptic plasticity.

The Journal of Neuroscience, January 21, 2004 • 24(3):722–732

Menthol-Induced Ca^{2+} Release from Presynaptic Ca^{2+} Stores Potentiates Sensory Synaptic Transmission

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Menthol and many of its derivatives produce profound sensory and mental effects. The receptor for menthol has been cloned and named cold- and menthol-sensitive receptor-1 (CMR1) or transient receptor potential channel M8 (TRPM8AQ: A) receptor. Using a dorsal root ganglion (DRG) and dorsal horn (DH) coculture system as a model for the first sensory synapse in the CNS, we studied menthol effects on sensory synaptic transmission and the underlying mechanisms. We found that menthol increased the frequency of miniature EPSCsAQ: B (mEPSCs). The effects persisted under an extracellular Ca^{2+}-free condition but were abolished by intracellular BAPTA and pretreatment with thapsigargin. Menthol-induced increases of mEPSC frequency were blocked by 2-aminoethoxydiphenylborane (2-APB) but not affected by the phospholipase C inhibitor U73122 or by the cADP receptor inhibitor 8-bromo-cADPR (8Br-cADPR)AQ: C. Double-patch recordings from DRG–DH pairs showed that menthol could potentiate evoked EPSCs (eEPSCs) and change the paired-pulse ratio of eEPSCs. A Ca^{2+} imaging study on DRG neurons demonstrated that menthol could directly release Ca^{2+} from intracellular Ca^{2+} stores. Menthol-induced Ca^{2+} release was abolished by 2-APB but not affected by U73122 or 8Br-cADPR. Taken together, our results indicate that menthol can act directly on presynaptic Ca^{2+} stores of sensory neurons to release Ca^{2+}, resulting in a facilitation of glutamate release and a modulation of neuronal transmission at sensory synapses. Expression of TRPM8 receptor on presynaptic Ca^{2+} stores, a novel localization for this ligand-gated ion channel, is also strongly suggested.

The Journal of Neuroscience, January 21, 2004 • 24(3):762–771

DEVELOPMENT/PLASTICITY/REPAIR

The Development of Mother–Infant Interactions after Neonatal Amygdala Lesions in Rhesus Monkeys

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As part of ongoing studies on the neurobiology of socioemotional behavior in the nonhuman primate, we examined the development of mother–infant interactions in 24 macaque monkeys who received either bilateral amygdala or hippocampus ibotenic acid lesions, or a sham surgical procedure at 2 weeks of age. After surgery, the infants were returned to their mothers and reared with daily access to small social groups. Behavioral observations of the infants in dyads (mother–infant pairs alone), tetrads (two mother–infant pairs), and social groups (six mother–infant pairs and one adult male) revealed species-typical mother–infant interactions for all lesion conditions, with the exception of increased physical contact time between the amygdala-lesioned infants and their mothers. Immediately after permanent separation from their mothers at 6 months of age, the infants were tested in a mother preference test that allowed the infants to choose between their mother and another familiar adult female. Unlike control and hippocampus-lesioned infants, the amygdala-lesioned infants did not preferentially seek proximity to their mother, nor did they produce distress vocalizations. Given the normal development of mother–infant interactions observed before weaning, we attribute the behavior of the amygdala-lesioned infants during the preference test to an impaired ability to perceive potential danger (i.e., separation from their mother in a novel environment), rather than to a disruption of the mother–infant relationship. These results are consistent with the view that the amygdala is not essential for fundamental aspects of social behavior but is necessary to evaluate potentially dangerous situations and to coordinate appropriate behavioral responses.

The Journal of Neuroscience, January 21, 2004 • 24(3):711–721

Heterogeneous Requirement of NGF for Sympathetic Target Innervation *In Vivo*

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The neurotrophin nerve growth factor (NGF) plays a crucial role in the development of the sympathetic nervous system. In addition to being required for sympathetic neuron survival *in vivo* and *in vitro*, NGF has been shown to mediate axon growth *in vitro*. The role of NGF in sympathetic axon growth *in vivo*, however, is not clear because of its requirement for survival. This requirement can be circumvented by a concomitant deletion of *Bax*, a pro-apoptotic Bcl-2 family member, thus allowing an examination of the role of neurotrophins in axon growth independently of their function in cell survival. Here, we analyzed peripheral sympathetic target organ innervation in mice deficient for both *NGF* and *Bax*.AQ: A In neonatal $NGF^{-/-}; Bax^{-/-}$ mice, sympathetic target innervation was absent in certain organs (such as salivary glands), greatly reduced in others (such as heart), somewhat diminished in a few (such as stomach and kidneys), but not significantly different from control in some (such as trachea). At embryonic day 16.5, peripheral target sympathetic innervation was also reduced *in* $NGF^{-/-}; Bax^{-/-}$ mice, with analogous variability for different organs. Interestingly, in some organs such as the spleen the precise location at which sympathetic axons become NGF-dependent for growth was evident. We thus show that NGF is required for complete peripheral innervation of both paravertebral and prevertebral sympathetic ganglia targets *in vivo* independently of its requirement for cell survival. Remarkably, target organs vary widely in their individual NGF requirements for sympathetic innervation.

The Journal of Neuroscience, January 21, 2004 • 24(3):743–751

Locus Ceruleus Activation Initiates Delayed Synaptic Potentiation of Perforant Path Input to the Dentate Gyrus in Awake Rats: A Novel β-Adrenergic- and Protein Synthesis-Dependent Mammalian Plasticity Mechanism

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Norepinephrine, acting through β-adrenergic receptors, is implicated in mammalian memory. In *in vitro* and *in vivo* studies, norepinephrine produces potentiation of the perforant path– dentate gyrus evoked potential; however, the duration and dynamics of norepinephrine-induced potentiation have not been explored over extended time periods. To characterize the long-term effects of norepinephrine on granule cell plasticity, the present study uses glutamatergic activation of the locus ceruleus (LC) to induce release of norepinephrine in the hippocampus of the awake rat and examines the subsequent modulation of the dentate gyrus evoked potential for 3 hr (short term) and 24 hr (long term) after LC activation. LC activation initiates a potentiation of the field EPSP slope observed 24 hr later. This late-phase potentiation of the synaptic potential is not preceded by early phase potentiation, although spike potentiation can be seen both immediately after, and 24 hr after, LC activation. Intracerebroventricular infusion of the β-adrenergic antagonist, propranolol, or the protein synthesis inhibitor, anisomycin, before LC activation blocks the potentiation of perforant path input observed at 24 hr. The initiation of late-phase synaptic potentiation observed at 24 hr but not at the 3 hr after LC activation parallels the observation of a cAMP- and protein synthesis-dependent long-lasting synaptic facilitation in *Aplysia* that is not preceded by short-term synaptic facilitation. Locus ceruleus-initiated synaptic potentiation may selectively support long-term, rather than short-term, memory. The observation of selective initiation of long-term synaptic facilitation in a mammalian brain, as in invertebrates, is additional evidence that these two forms of memory depend on separable biological mechanisms.
The Journal of Neuroscience, January 21, 2004 • 24(3):598 – 604

The Transition from Development to Motor Control Function in the Corticospinal System

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During early postnatal development, corticospinal (CS)AQ: A system stimulation, electrical or transcranial magnetic, is minimally effective in producing muscle contraction, despite having axon terminals that excite spinal neurons. Later, after stimulation becomes more effective, the cortical motor representation develops, and movements the system controls in maturity are expressed. We determined whether development of temporal facilitation (response enhancement produced by the second of a pair of pyramidal tract stimuli, or a higher stimulus multiple of a train of stimuli)AQ: B correlated with these changes. Facilitation of the monosynaptic CS response was larger in older kittens and adults than younger kittens. When facilitation was strong, strong motor responses were evoked by pyramidal stimulation with small currents and few pulses. With strong facilitation in older kittens, corticospinal axon varicosities colocalize synaptophysin like adults, suggesting a presynaptic mechanism. With effective facilitation, control signals from the cortex can be sufficiently effective to provoke muscle contraction for guiding movements.
The Journal of Neuroscience, January 21, 2004 • 24(3):605– 614

Cortical Synaptogenesis and Motor Map Reorganization Occur during Late, But Not Early, Phase of Motor Skill Learning

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Extensive motor skill training induces reorganization of movement representations and synaptogenesis within adult motor cortex. Motor skill does not, however, develop uniformly across training sessions. It is characterized by an initial fast phase, followed by a later slow phase of learning. How cortical plasticity emerges during these phases is unknown. Here, we examine motor map topography and synapse number within rat motor cortex during the early and late phases of motor learning. Adult rats were placed in either a skilled or unskilled reaching condition (SRC and URC, respectively) for 3, 7, or 10 d. Intracortical microstimulation of layer V was used to determine the topography of forelimb movement representations within caudal forelimb area of motor cortex contralateral to the trained paw. Quantitative electron microscopy was used to measure the number of synapses per neuron within layer V. SRC animals showed significant increases in reaching accuracy after 3, 7, and 10 d of training. In comparison with URC animals, SRC animals had significantly larger distal forelimb representations after 10 d of training only. Furthermore, SRC animals had significantly more synapses per neuron than URC animals after 7 and 10 d of training. These results show that both motor map reorganization and synapse formation occur during the late phase of skill learning. Furthermore, synaptogenesis precedes map reorganization. We propose that motor map reorganization and synapse formation do not contribute to the initial acquisition of motor skills but represent the consolidation of motor skill that occurs during late stages of training.
The Journal of Neuroscience, January 21, 2004 • 24(3):628 – 633

Columnar Specificity of Microvascular Oxygenation and Volume Responses: Implications for Functional Brain Mapping

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Cortical neurons with similar properties are grouped in columnar structures and supplied by matching vascular networks. The hemodynamic response to neuronal activation, however, is not well described on a fine spatial scale. We investigated the spatiotemporal characteristics of microvascular responses to neuronal activation in rat barrel cortex using optical intrinsic signal imaging and spectroscopy. Imaging was performed at 570 nm to provide functional maps of cerebral blood volume (CBV) changes and at 610 nm to estimate oxygenation changes. To emphasize parenchymal rather than large vessel contributions to the functional hemodynamic responses, we developed an ANOVA-based statistical analysis technique. Perfusion-based maps were compared with underlying neuroanatomy with cytochrome oxidase staining. Statistically determined CBV responses localized accurately to individually stimulated barrel columns and could resolve neighboring columns with a resolution better than 400 μm. Both CBV and early oxygenation responses extended beyond anatomical boundaries of single columns, but this vascular point spread did not preclude spatial specificity. These results indicate that microvascular flow control structures providing targeted flow increases to metabolically active neuronal columns also produce finely localized changes in CBV. This spatial specificity, along with the high contrast/noise ratio, makes the CBV response an attractive mapping signal. We also found that functional oxygenation changes can achieve submillimeter specificity not only during the transient deoxygenation ("initial dip") but also during the early part of the hyperoxygenation. We, therefore, suggest that to optimize hemodynamic spatial specificity, appropriate response timing (using $\leq$2–3 sec changes) is more important than etiology (oxygenation or volume).

The Journal of Neuroscience, January 21, 2004 • 24(3):634 – 641

Changes in the Effect of Spinal Prostaglandin E_2 during Inflammation: Prostaglandin E (EP1–EP4) Receptors in Spinal Nociceptive Processing of Input from the Normal or Inflamed Knee Joint

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Inflammatory pain is caused by sensitization of peripheral and central nociceptive neurons. Prostaglandins substantially contribute to neuronal sensitization at both sites. Prostaglandin E_2 (PGE_2) applied to the spinal cord causes neuronal hyperexcitability similar to peripheral inflammation. Because PGE_2 can act through EP1AQ: A–EP4 receptors, we addressed the role of these receptors in the spinal cord on the development of spinal hyperexcitability. Recordings were made from nociceptive dorsal horn neurons with main input from the knee joint, and responses of the neurons to noxious and innocuous stimulation of the knee, ankle, and paw were studied afterAQ: B spinal application of recently developed specific EP1–EP4 receptor agonists. Under normal conditions, spinal application of agonists at EP1, EP2, and EP4 receptors induced spinal hyperexcitability similar to PGE_2. Interestingly, the effect of spinal EP receptor activation changed during joint inflammation. When the knee joint had been inflamed 7–11 hr before the recordings, only activation of the EP1 receptor caused additionalAQ: C facilitation, whereas spinal application of EP2 and EP4 receptor agonists had no effect. Additionally, an EP3α receptor agonist reduced responses to mechanical stimulation. The latter also attenuated spinal hyperexcitability induced by spinal PGE_2. In isolated DRG neurons, the EP3α agonist reduced the facilitatory effect of PGE_2 on TTX-resistant sodium currents. Thus pronociceptive effects of spinal PGE_2 can be limited, particularly under inflammatory conditions, through activation of an inhibitory splice variant of the EP3 receptor. The latter might be an interesting target for controlling spinal hyperexcitability in inflammatory pain states.

The Journal of Neuroscience, January 21, 2004 • 24(3):642– 651

Coordinate Synaptic Mechanisms Contributing to Olfactory Cortical Adaptation

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Anterior piriform cortex (aPCX) neurons rapidly filter repetitive odor stimuli despite relatively maintained input from mitral cells. This cortical adaptation is correlated with short-term depression of afferent synapses, *in vivo*. The purpose of this study was to elucidate mechanisms underlying this nonassociative neural plasticity using *in vivo* and *in vitro* preparations and to determine its role in cortical odor adaptation. Lateral olfactory tract (LOT)-evoked responses were recorded in rat aPCX coronal slices. Extracellular and intracellular potentials were recorded before and after simulated odor stimulation of the LOT. Results were compared with *in vivo* intracellular recordings from aPCX layer II/III neurons and field recordings in urethane-anesthetized rats stimulated with odorants. The onset, time course, and extent of LOT synaptic depression during both *in vitro* electrical and *in vivo* odorant stimulation methods were similar. Similar to the odor specificity of cortical odor adaptation *in vivo*, there was no evidence of heterosynaptic depression between independent inputs *in vitro*. *In vitro* evidence suggests at least two mechanisms contribute to this activity-dependent synaptic depression: a rapidly recovering presynaptic depression during the initial 10–20 sec of the post-train recovery period and a longer lasting ($\sim$120 sec) depression that can be blocked by the metabotropic glutamate receptor (mGluR) II/III antagonist (*RS*)-α-cyclopropyl-4-phosphonophenylglycine (CPPG) and by the β-adrenergic receptor agonist isoproterenol. Importantly, in line with the *in vitro* findings, both adaptation of odor responses in the β (15–35 Hz) spectral range and the associated synaptic depression can also be blocked by intracortical infusion of CPPG *in vivo*.

The Journal of Neuroscience, January 21, 2004 • 24(3):652– 660

Firing Patterns of Type II Spiral Ganglion Neurons *In Vitro*

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Type I and type II spiral ganglion neurons convey auditory information from the sensory receptors in the cochlea to the CNS. The numerous type I neurons have been extensively characterized, but the small population of type II neurons with their unmyelinated axons are undetectable with most recording methods. Despite the paucity of information about the type II neurons, it is clear that they must have a significant role in sound processing because they innervate the large number of outer hair cells that are critical for maintaining normal responses to stimuli. To elucidate the function of type II neurons, we have developed an approach for studying their electrophysiological features *in vitro*.

Type II neurons obtained from postnatal day 6–7 mice displayed distinctly different firing properties than type I neurons. They showed slower accommodation, lower action potential thresholds, and more prolonged responses to depolarizing current injection than the type I neurons. These differences were most evident in neurons from the basal, high-frequency region of the cochlea. The basal type I neurons displayed uniformly fast firing features, whereas the basal type II neurons showed particularly slow accommodation and responses to depolarization. Interestingly, neurons from the apical, low-frequency region of the cochlea showed the opposite trend. These data suggest that the type I and type II neurons have specialized electrophysiological characteristics tailored to their different roles in auditory signal processing. In particular, the type II neuron properties are consistent with cells in other sensory systems that receive convergent synaptic input for high-sensitivity stimulus detection.
The Journal of Neuroscience, January 21, 2004 • 24(3):733–742

Posterior Triangular Thalamic Neurons Convey Nociceptive Messages to the Secondary Somatosensory and Insular Cortices in the Rat

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This study investigated the responses of posterior triangular (PoT) thalamic neurons to tactile and noxious calibrated stimuli in anesthetized rats. We report here that 41% of PoT units responded to cutaneous stimulation, in most cases, by increasing strongly their firing. Forty-five percent of the responding units were nociceptive specific (NS), 19% were nociceptive nonspecific (NNS), and 36% were tactile. The NS units responded only to frankly noxious stimuli applied to relatively large receptive fields (several parts of the body). They encoded nociceptive temperatures chiefly in 46–50°C ranges. The NNS units resembled NS units but also responded to innocuous stimuli. Tactile units responded chiefly to repeated innocuous stimuli applied to very small receptive fields (one to two fingers or vibrissae).

A representative sample of PoT somatosensory neurons, characterized first by their response to innocuous and noxious cutaneous stimuli, were filled with juxtacellular injection of biotin–dextran that made it possible to label adequately the soma, the dendrites, and the entire axon of PoT neurons. We observed that the axons of NS neurons terminated only in secondary somatosensory (S2) cortex, whereas the axons of NNS and tactile neurons projected chiefly to the insular cortex and the amygdala.

In conclusion, our results demonstrate a spinal–PoT–S2/insular cortices nociceptive pathway that conveys nociceptive messages arising from lamina I and spinal neurons of deep laminas. Furthermore, our results demonstrate for the first time that projections of PoT neurons are correlated to their physiological properties.
The Journal of Neuroscience, January 21, 2004 • 24(3):752–761

NEUROBIOLOGY OF DISEASE

Neurons and Astrocytes Respond to Prion Infection by Inducing Microglia Recruitment

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The accumulation and activation of microglial cells at sites of amyloid prion deposits or plaques have been documented extensively. Here, we investigate the *in vivo* recruitment of microglial cells soon after intraocular injection of scrapie-infected cell homogenate (hgtsc$^+$) using immunohistochemistry on retinal sections. A population of CD11b/CD45-positive microglia was specifically detected within the ganglion and internal plexiform retinal cell layers by 2 d after intravitreal injection of hgtsc$^+$. Whereas no chemotactism properties were ascribed to hgtsc$^+$ alone, a massive migration of microglial cells was observed by incubating primary cultured neurons and astrocytes with hgtsc$^+$ in a time- and concentration-dependent manner. hgtsc$^+$ triggered the recruitment of microglial cells by interacting with both neurons and astrocytes by upregulation of the expression levels of a broad spectrum of neuronal and glial chemokines. We show that, *in vitro* and *in vivo*, the microglia migration is at least partly under the control of chemokine receptor-5 (CCR-5) activation, because highly specific CCR-5 antagonist TAK-779 significantly reduced the migration rate of microglia. Activated microglia recruited in the vicinity of prion may, in turn, cause neuronal cell damage by inducing apoptosis. These findings provide insight into the understanding of the cell–cell communication that takes place during the development of prion diseases.
The Journal of Neuroscience, January 21, 2004 • 24(3):620–627

Role of Matrix Metalloproteinases in Delayed Neuronal Damage after Transient Global Cerebral Ischemia

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Mechanisms of selective neuronal death in the hippocampus after global cerebral ischemia remain to be clarified. Here, we explored a possible role for matrix metalloproteinases (MMPs) in this phenomenon. Although many studies have demonstrated detrimental roles for the gelatinase MMP-9 in focal cerebral ischemia, how dysregulated MMP proteolysis influences global cerebral ischemia is less well understood. In this study, CD-1 mice were subjected to transient global ischemia. Transient occlusions of common carotid arteries for periods between 20 and 40 min led to increasing hippocampal neuronal death after 3 d. Gel zymography showed elevations in gelatinase (MMP-2 and MMP-9) activity. *In situ* zymography showed that gelatinase activity was mostly colocalized with neuron-specific nuclear proteinAQ: A-stained pyramidal neurons. Mice treated with the broad-spectrum metalloproteinase inhibitor BB-94 (50 mg/kg, i.p.) showed reduced hippocampal gelatinase activity after transient global cerebral ischemia and suffered significantly reduced hippocampal neuronal damage compared with vehicle-treated controls ($p < 0.01$). Additionally, hippocampal gelatinase activity and neuronal damage after transient global ischemia were also significantly reduced in MMP-9 knock-out mice compared with wild-type mice ($p < 0.05$). These data indicate a potential deleterious role for MMP-9 in the pathogenesis of delayed neuronal damage in the hippocampus after global cerebral ischemia.

The Journal of Neuroscience, January 21, 2004 • 24(3):671–678

Overexpression of Adenosine Kinase in Epileptic Hippocampus Contributes to Epileptogenesis

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Endogenous adenosine in the brain is thought to prevent the development and spread of seizures via a tonic anticonvulsant effect. Brain levels of adenosine are primarily regulated by the activity of adenosine kinase. To establish a link between adenosine kinase expression and seizure activity, we analyzed the expression of adenosine kinase in the brain of control mice and in a kainic acid-induced mouse model of mesial temporal lobe epilepsy. Immunohistochemical analysis of brain sections of control mice revealed intense staining for adenosine kinase, mainly in astrocytes, which were more or less evenly distributed throughout the brain, as well as in some neurons, particularly in olfactory bulb, striatum, and brainstem. In contrast, hippocampi lesioned by a unilateral kainic acid injection displayed profound astrogliosis and therefore a significant increase in adenosine kinase immunoreactivity accompanied by a corresponding increase of enzyme activity, which paralleled chronic recurrent seizure activity in this brain region. Accordingly, seizures and interictal spikes were suppressed by the injection of a low dose of the adenosine kinase inhibitor 5-iodotubercidin. We conclude that overexpression of adenosine kinase in discrete parts of the epileptic hippocampus may contribute to the development and progression of seizure activity.

The Journal of Neuroscience, January 21, 2004 • 24(3):692–701

Neural Bases of Set-Shifting Deficits in Parkinson's Disease

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Patients with Parkinson's disease (PD) exhibit impairments in several cognitive functions similar to those observed in patients with prefrontal cortex (PFC) lesions. The physiological origins of these cognitive deficits are not well documented. Two mechanisms have been proposed: disruptions in corticostriatal circuits or a deficiency in frontal dopamine. We previously used functional magnetic resonance imaging (fMRI) in young healthy subjects to separate patterns of PFC and striatum activity during distinct phases of performance of the Wisconsin Card Sorting Task, a set-shifting task that reveals deficits in patients with PD. Here, the same fMRI protocol was used in PD patients and matched controls. Decreased activation was observed in the PD group compared with the matched control group in the ventrolateral PFC when receiving negative feedback and the posterior PFC when matching after negative feedback. In controls, these prefrontal regions specifically coactivated with the striatum during those stages of task performance. In contrast, greater activation was found in the PD group compared with the matched control group in prefrontal regions, such as the posterior and the dorsolateral PFC when receiving positive or negative feedback, that were not coactivated with the striatum in controls. These results suggest that both nigrostriatal dopamine depletion and intracortical dopamine deficiency may play a role in cognitive deficits in PD, depending on the involvement of the striatum in the task at hand.

The Journal of Neuroscience, January 21, 2004 • 24(3):702–710