This Week in The Journal

Cellular/Molecular

Neurosteroids and Tonic GABAergic Inhibition

Jamie Maguire and Istvan Mody

(see pages 2155–2162)

Fluctuations in progesterone levels during the ovarian cycle can alter the subunit composition of $GABA_A$ receptors. In this week's *Journal*, Maguire and Mody link this effect to neurosteroid production. The authors focused on the δ subunit that underlies GABA-mediated tonic inhibition of dentate granule cells in the hippocampus. The progesterone receptor antagonist RU486 had no effect on $GABA_A$ subunit expression in cycling mice. However, finasteride, which inhibits synthesis of neurosteroids from progesterone, prevented upregulation of the δ subunit and blocked the enhancement of $GABA_A$ receptor-mediated tonic inhibition that normally occurs during diestrous. Similar effects were seen in males or ovariectomized females that were treated with progesterone, as well as in mice subjected to an acute stress (2 min of increased CO_2). Acute stress increases neurosteroids, and treatment of brain slices with the neurosteroid THDOC (3α,5α-tetrahydrodeoxycorticosterone) also increased tonic GABAergic inhibition.

Development/Plasticity/Repair

Engineering Astrocytes as Injury Repairmen

William B. J. Cafferty, Shih-Hung Yang, Philip J. Duffy, Shuxin Li, and Stephen M. Strittmatter

(see pages 2176–2185)

Unfortunately, the CNS throws up a number of roadblocks to axonal regeneration. One of these, chondroitin sulfate proteoglycans (CSPGs), is a major component of the glial scar that forms at the site of a CNS injury. This week, Cafferty et al. exploit the bacterial enzyme chondroitinase ABC (ChABC), which can digest CSPGs, to reopen the roadway. The authors made a transgenic mouse that expressed ChABC in astrocytes under the control of the *gfap* promoter. After dorsal hemisection of the spinal cord, corticospinal tract axons in wild-type mice stopped abruptly rostral to the lesion. In the transgenic mice, however, axons extended into the lesion, but motor function was not improved. However, after dorsal rhizotomy, axons of sensory neurons grew back through the dorsal root entry zone and into the CNS and also improved sensory function. The next CNS regeneration strategy may be to combine ChABC with targeting of myelin-associated inhibitors.

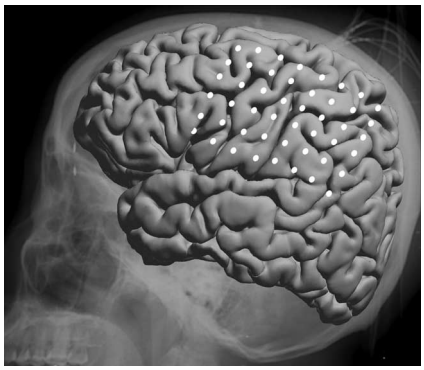
Behavioral/Systems/Cognitive

The Homunculus, Up Close and Personal

Kai J. Miller, Eric C. Leuthardt, Gerwin Schalk, Rajesh P. N. Rao, Nicholas R. Anderson, Daniel W. Moran, John W. Miller, and Jeffrey G. Ojemann

(see pages 2424–2432)

When it comes to recording of cortical activity, the closer one is to the source, the better the information. This week, Miller et al. used subdural grid electrodes over sensorimotor cortex to examine electrocorticographic (ECoG) signals associated with motor movements. Their subjects were patients awaiting epilepsy surgery who had intracranial electrode arrays in place to assist seizure localization. Voluntary movements of the tongue, hand, or other body parts produced spectral shifts in areas corresponding to the classical homunculus. The authors used the data from 22 subjects to create maps of cortical activity in different frequency ranges. In the low-frequency band (LFB) (8–32 Hz), movements reduced the signal amplitudes at 20–30 Hz, whereas in the high-frequency band (HFB) (76–100 Hz), movements increased the EcoG. The HFB signals represented activity that was more local than the LFB signals. The high fidelity of the EcoG may make it a useful complement to other methods of functional brain mapping.



A grid of subdural electrodes (white dots) can be seen on a lateral skull x ray in a patient undergoing evaluation for epilepsy surgery. The grid was placed over the sensorimotor cortex as shown with standardized brain template. See the article by Miller et al. for details.

Neurobiology of Disease

A Forward Genetic Screen in Mice for Recessive Deafness

Martin Schwander, Anna Sczaniecka, Nicolas Grillet, Janice S. Bailey, Matthew Avenarius, Hossein Najmabadi, Brian M. Steffy, Glenn C. Federe, Erica A. Lagler, Raheleh Banan, Rudy Hice, Laura Grabowski-Boase, Elisabeth M. Keithley, Allen F. Ryan, Gary D. Housley, Tim Wiltshire, Richard J. H. Smith, Lisa M. Tarantino, and Ulrich Müller

(see pages 2163–2175)

This week, Schwander et al. take a step forward in the pursuit of recessive genes for deafness. The authors undertook a forward genetics screen by exposing male mice to the mutagen ENU (*N*-ethyl-*N*-nitrosourea) and then breeding them with wild-type females. Fifty-one of 850 pedigrees analyzed had impaired acoustic startle response, and 19 of the 51 had abnormal auditory thresholds. Fourteen of 19 lines showed recessive inheritance patterns. The authors have thus far identified hair cell defects attributable to point mutations in four genes, all of which have been linked to deafness in humans. Human missense mutations in one gene, *pejvakin* produce a nonprogressive auditory neuropathy as a result of defects in auditory nerve cells. In contrast, the mutation identified in this screen introduced a stop codon in *pejvakin*. This mutation resulted in progressive hearing loss caused by outer hair cell malfunction, suggesting distinct functions of this gene in neurons and hair cells.