This Week in The Journal

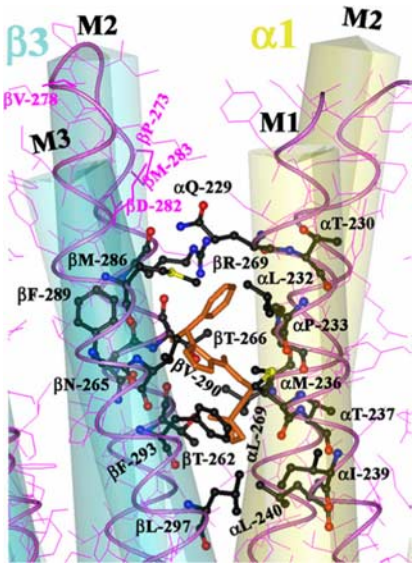
● Cellular/Molecular

Intersubunit Anesthetic Binding on $GABA_A$ Receptors

Guo-Dong Li, David C. Chiara, Gregory W. Sawyer, S. Shaukat Husain, Richard W. Olsen, and Jonathan B. Cohen

(see pages 11599–11605)

Anesthesia has revolutionized medicine since its introduction in 1846. But the molecular workings of the responsible agents have remained surprisingly elusive. This week, Li et al. tackled the problem using photoaffinity labeling, a technique for labeling binding sites on proteins. Because most general anesthetics enhance the activity of $GABA_A$ receptors, the authors photolabeled $GABA_A$ receptors, purified from bovine cortex, with a photoreactive analog of the intravenous anesthetic etomidate. By protein microsequencing, they identified two labeled methionines. $GABA_A$ receptors are heteromers of five subunits each having extracellular domains and four membrane-spanning domains (M1–4). One photolabeled methionine was in the M1 region of the α subunit and the other was in M3 of the β subunit. Structural models predict that the anesthetic site is a water-filled pocket located in the same subunit interface as the GABA binding site in the extracellular domain, some 50 Å away. The perfect place for an allosteric modulatory site, it would seem.



A portion of the $GABA_A$ receptor homology model showing the intersubunit anesthetic binding pocket between the β3 and α1 subunit. The bound etomidate analog (gold) is in contact with residues identified by photoaffinity labeling, αMet236 and βMet286. See Li et al. for details.

▲ Development/Plasticity/Repair

Transcranial Imaging of Visual Cortical Plasticity

Manavu Tohmi, Hiroki Kitaura, Seiji Komagata, Masaharu Kudoh, and Katsuei Shibuki

(see pages 11775–11785)

Several tricks have been used to map brain activity noninvasively, thus avoiding potentially toxic dyes and manipulation of the tissue. This week, Tohmi et al. report on a noninvasive imaging technique that is powered by mitochondria. The authors compared the well studied intrinsic optical imaging method to that of endogenous flavoprotein fluorescence, the latter of which relies on activity-induced changes in the fluorescence of mitochondrial flavoproteins. The authors measured transcranial fluorescence in the visual cortex of anesthetized mice before and after one eye had been sewn shut for days or weeks. As expected, monocular deprivation led to decreased light responses from the deprived eye, whereas responses from the nondeprived eye increased in the binocular, but not the monocular, zone of the cortex. Imaging by endogenous flavoprotein fluorescence proved to be superior to imaging of intrinsic signals both in terms of signal-to-noise ratio and temporal resolution.

■ Behavioral/Systems/Cognitive

Probing Cerebellar Granule Cell Function In Vivo

Henrik Jörntell and Carl-Fredrik Ekerot

(see pages 11786–11797)

Often the simplest explanation can be the best one. Jörntell and Ekerot argue that this is the case for the way in which cerebellar granule cells process somatosensory information. A granule cell has about four dendrites, each receiving input from a single excitatory mossy fiber synapse, which in turn transmits signals from a specific site (or receptive field) on the skin. The authors recorded synaptic activity in granule cells in the forelimb area of the cerebellar C3 zone in decerebrate/unanesthetized cats after different types of skin stimulation. Each mossy fiber input to a granule cell contributed to spiking. There was little evidence of convergence from different types of inputs or from different receptive fields. In other words, these granule cells did not integrate different types of inputs, as has been proposed in sparse-coding theories, but rather acted as signal-to-noise-enhancing threshold detectors for a single, specific type of input.

♦ Neurobiology of Disease

Altered AMPA Receptor Trafficking and ALS

Chen Lai, Chengsong Xie, Stefanie G. McCormack, Hsueh-Cheng Chiang, Marta K. Michalak, Xian Lin, Jayanth Chandran, Hoon Shim, Mika Shimoji, Mark R. Cookson, Richard L. Huganir, Jeffrey D. Rothstein, Donald L. Price, Philip C. Wong, Lee J. Martin, J. Julius Zhu, and Huaibin Cai

(see pages 11798–11806)

Loss-of-function mutations in the *ALS2* gene cause a juvenile form of amyotrophic lateral sclerosis, resulting in a progressive loss of motor neurons. This week, Lai et al., using a combination of molecular and electrophysiological approaches, found that loss of the *ALS2* gene product alsin in $ALS2^{-/-}$ mice causes defects in AMPA receptor trafficking. When Lai et al. looked for proteins that interact with alsin, they fished out the glutamate receptor interacting protein 1 (GRIP1), whose role is to shuttle the AMPA receptor subunit GluR2 to the postsynaptic membrane. In neurons from $ALS2^{-/-}$ mice, neither GRIP1 nor GluR2-containing AMPA receptors made their way to the synapse. This is not inconsequential because AMPA receptors lacking GluR2 subunits are more permeable to calcium, which rendered neurons more vulnerable to excitotoxicity. Thus, impaired AMPA trafficking in the absence of normal alsin could contribute to motor neuron degeneration.