This Week in The Journal

● Cellular/Molecular

Glycine Receptor Activation: When Three Out of Five Is Enough

Marco Beato, Paul J. Groot-Kormelink, David Colquhoun, and Lucia G. Sivilotti
(see pages 895–906)

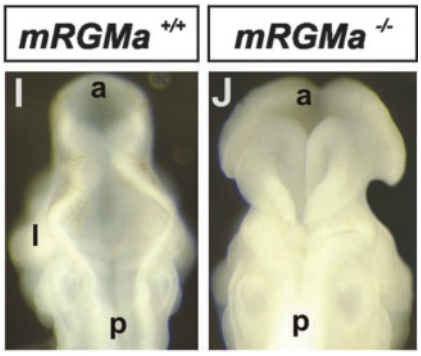
The prototypic member of the acetylcholine receptor family, the muscle nicotinic receptor, is a heteromeric complex with five subunits but only two ligand-binding sites. However, some members of this receptor superfamily are homomeric, containing five seemingly identical binding sites. Whether activation actually requires binding of five agonist molecules in this situation is unclear. Such questions cannot be answered using classical pharmacological methods. Thus Beato et al. analyzed the single-channel activity of recombinant glycine receptors containing five α1 subunits, the principal juvenile form of this inhibitory synaptic receptor. The channels opened more efficaciously as the glycine concentration increased, but gating saturated when three glycine molecules were bound. They could not resolve whether the fourth and fifth bindings occur or are silent. The three out of five odds may be a general rule, because similar results have been suggested for homomeric $GABA_C$ and 5-HT3 channels.

▲ Development/Plasticity/Repair

The Mouse Repulsive Guidance Molecule (RGM) Family

Vera Niederkofler, Rishard Salie, Markus Sigrist, and Silvia Arber
(see pages 808–818)

Topographically organized axonal projections are guided by gradients of attractive and repulsive molecules, an idea first espoused by Roger Sperry to explain the pattern of retinal ganglia cell termination zones in the chick optic tectum. The search for molecules expressed in such patterns led to the Ephrins and the less-characterized chick repulsive guidance molecule (cRGM). In an effort to define an *in vivo* role for RGM, Niederkofler et al. have now identified three mouse homologs. Mouse RGMa (mRGMa) and mRGMb were expressed in a nonoverlapping pattern in the nervous system, whereas mRGMc was confined to skeletal muscle. Despite its expression in the superior colliculus, mRGMa is not essential for patterning of ganglion termination zones, as demonstrated by normal retinotectal mapping in mRGMa-deficient mice. Instead, one-half of the mRGMa-deficient embryos were exencephalic (they failed to close the neural tube), suggesting a more significant role in early development. The latter function appears to be a role shared with the Ephrins.



Dorsal head view of embryonic day 10.5 mice showing exencephalic phenotype in mRGMa-deficient mice (*J*) compared with wild-type mice (*I*).

■ Behavioral/Systems/Cognitive

Painful Memories

Thomas Klein, Walter Magerl, Hanns-Christian Hopf, Jürgen Sandkühler, and Rolf-Detlef Treede
(see pages 964–971)

Long-term potentiation (LTP) and long-term depression (LTD) are among the best-studied examples of synaptic plasticity. These lasting changes in synaptic efficacy are candidate mechanisms for learning and memory, but there is little definitive evidence linking these cellular mechanisms to human behavior. In this week's *Journal*, Klein et al. build on observations that high- or low-frequency electrical stimulation induces LTP- and LTD-like phenomena in spinal nociceptive pathways in animals. They focused on a behavioral correlate that is easy to evoke and measure in humans: pain. While both stimulation patterns led to a corresponding change in perception (hyperalgesia with LTP-like stimuli and hypoalgesia with LTD-like stimuli), the specific outcomes and mechanisms differed subtly. Although the underlying mechanisms may be complex, these results add to the idea that LTP-like plasticity contributes to hyperalgesia and chronic pain, whereas LTD-like plasticity may contribute to the analgesia associated with treatments such as transcutaneous electric nerve stimulation (TENS) and perhaps its ancient relative, acupuncture.

♦ Neurobiology of Disease

CRE, Transcription, and HD

Karl Obrietan and Kari R. Hoyt
(see pages 791–796)

The neurodegeneration in Huntington's disease (HD) has been linked to polyglutamine repeats in the huntingtin protein. The consequences of this mutation, and indeed the normal function of the protein, remain a mystery. Recently, *in vitro* evidence suggested that huntingtin-related intranuclear inclusions interfere with cAMP-response element (CRE)-mediated gene transcription, presumably by binding of mutant huntingtin with CREB-binding protein (CBP). However, in this issue Obrietan and Hoyt report facilitated gene transcription in an HD animal *in vivo*. They crossed an HD mouse with a mouse that expressed a CRE-dependent marker protein. In addition to increased CRE-mediated marker expression (notably in the striatum), the HD mice also expressed elevated amounts of phosphorylated CREB and a CREB-regulated protein. Intracellular inclusions were present in the HD mice; thus they were not sufficient to prevent transcription or translation. Why the discrepancy with previous reports? The authors wonder if high expression levels of huntingtin as used in the previous *in vitro* studies may allow a low-affinity interaction between CBP and huntingtin.