This Week in The Journal

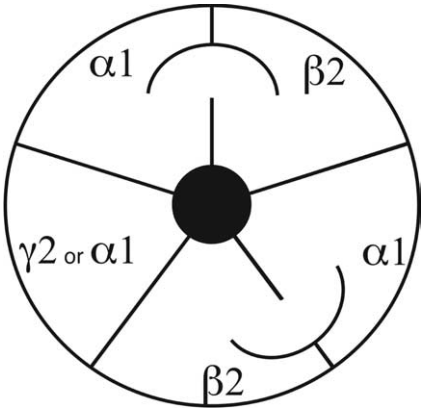
● Cellular/Molecular

Fixing the Stoichiometry of GABA$_A$ Receptors

Andrew J. Boileau, Robert A. Pearce, and Cynthia Czajkowski

(see pages 11219–11230)

GABA$_A$ receptor channels can assemble from multiple combinations of subunits, making it difficult to define the channel properties of any given subtype. To circumvent this problem, Boileau et al. hooked α1 and β2 subunit cDNAs in tandem ($\alpha\beta$tan) to constrain the stoichiometry of receptors expressed in human embryonic kidney 293 cells. Rapid application of agonist to outside-out membrane patches produced currents with properties of $\alpha1\beta2$ channels when $\alpha\beta$tan+α1 subunits were expressed or of $\alpha1\beta2\gamma2$ channels when $\alpha\beta$tan+γ2 subunits were expressed. The authors then tested the effect of the γ2-associated accessory protein GABA$_A$ receptor-associated protein (GABARAP) on channel properties. Coexpression of GABARAP with $\alpha\beta$tan+γ2 or with α1+β2+γ2 in a 1:1:10 ratio did not affect deactivation, desensitization, or benzodiazepine-induced potentiation. Coexpression with α1+β2+γ2 in a 1:1:0.5 ratio produced $\alpha1\beta2\gamma2$-like currents, suggesting that GABARAP does not directly alter channel properties but rather enhances surface expression of receptors containing a γ subunit.



Tandem GABA$_A$ receptor subunits, marked with an arc, were expressed alone or with free α1, β2, and γ2S subunits. See the article by Boileau et al. for details.

▲ Development/Plasticity/Repair

PLC and LTD in Visual Cortex

Se-Young Choi, Jeff Chang, Bin Jiang, Geun-Hee Seol, Sun-Seek Min, Jung-Soo Han, Hee-Sup Shin, Michela Gallagher, and Alfredo Kirkwood

(see pages 11433–11443)

Cortical circuits are shaped by sensory experiences that weaken some synaptic connections and strengthen others. NMDA receptors are necessary for the induction of long-term depression (LTD) in rodent visual cortex, but Choi et al. show this week that a threshold level of phospholipase C (PLC) activity is also required. α1 Adrenergic and M1 muscarinic receptors as well as the metabotropic glutamate receptor mGluR5 are coupled to PLC in visual cortex. When antagonists for all three receptors were bath applied together, LTD was blocked. Subsequently, the authors selectively lesioned cholinergic and noradrenergic neurons *in vivo* and then recorded from slices 2 weeks later after depletion of acetylcholine and noradrenaline. LTD could still be induced but was blocked by an mGluR5 antagonist. LTD was rescued by the addition of M1 muscarinic or α1 adrenergic agonists. Thus, activation of any of the three receptors provided sufficient PLC activity for LTD induction.

■ Behavioral/Systems/Cognitive

The Kiss(peptin) of Puberty

Seong-Kyu Han, Michelle L. Gottsch, Kathy J. Lee, Simina M. Popa, Jeremy T. Smith, Sonya K. Jakawich, Donald K. Clifton, Robert A. Steiner, and Allan E. Herbison

(see pages 11349–11356)

The suitably named neuropeptide, kisspeptin, and its G-protein-coupled receptor GPR54 are important in sexual maturation. Mutations or knock-out in the *GPR54* receptor gene cause sexual immaturity and infertility in humans and mice, respectively. This week, Han et al. show that kisspeptin directly and potently activates neurons that express gonadotropin-releasing hormone (GnRH). In perforated-patch-clamp recordings, kisspeptin depolarized >90% of GnRH neurons from the rostral preoptic area of adult male and female mice. The depolarizations were prolonged, presumably consistent with the high potency of the exogenous peptide. The responsiveness of GnRH neurons increased from 25% in juvenile animals to 50% in prepubertal animals. An increase in KiSS mRNA in the anteroventral periventricular area, the likely direct input to GnRH neurons, also increased during puberty. Central administration of kisspeptin evoked secretion of the gonadotropins *in vivo*, consistent with a signaling role for kisspeptin in the onset of puberty.

♦ Neurobiology of Disease

Seizures in a Mouse with Supersensitive Nicotinic Receptors

Carlos Fonck, Bruce N. Cohen, Raad Nashmi, Paul Whiteaker, Daniel A. Wagenaar, Nivalda Rodrigues-Pinguet, Purnima Deshpande, Sheri McKinney, Steven Kwoh, Jose Munoz, Cesar Labarca, Allan C. Collins, Michael J. Marks, and Henry A. Lester

(see pages 11396–11411)

Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) arises from mutations of the pore-forming M2 region of the α4 or β2 subunits of the nicotinic acetylcholine receptor, This week, Fonck et al. probed the phenotype caused by a leucine to alanine (L9′A) mutation in the mouse α4 subunit. As reported for other ADNFLE mutations in α4, L9′A channels expressed in *Xenopus* oocytes had a much higher affinity for acetylcholine. Mice heterozygous or homozygous for L9′A α4 channels were also much more sensitive to seizures caused by nicotine injections, although they did not have spontaneous seizures. Interestingly, nicotine pretreatment actually protected against evoked seizures, presumably because the mutant channels were highly desensitizing. Seizures in the mutant had the behavioral and EEG characteristics of partial seizures, perhaps suggesting an origin in limbic areas. The overall phenotype of these mice shares features with the human condition, suggesting that gain-of-function mutations underlie ADNFLE.