This Week in The Journal

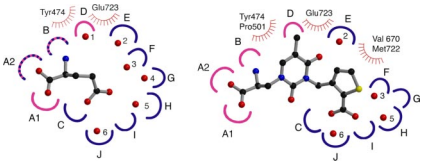
● Cellular/Molecular

Bending the Rules for Glutamate Receptors

Mark L. Mayer, Alokesh Ghosal, Nigel P. Dolman, and David E. Jane

(see pages 2852–2861)

This week, Mayer et al. literally stretch our structural understanding of ionotropic glutamate receptors (GluRs). The bilobed, clamshell configuration of the ligand-binding core of ionotropic glutamate receptors mostly has been investigated using S1S2 domains crystallized with agonist. The extracellular S1 and S2 domains envelop agonists with the extent of closure presumably important to channel gating. The authors report the crystal structure of the kainate receptor GluR5 bound to the novel, high-affinity antagonists UBP302 and UBP310. Crystal structures of GluR5–UBP complexes showed a much more open conformation than other glutamate receptors, with GluR5–UBP302 being the most extended. Although the authors were unable to crystallize the apo (unbound) or resting form of GluR5 S1S2, their results suggest that kainate receptors undergo much larger conformation shifts than has been suggested by structural studies of AMPA receptors. Interestingly, large movements are the norm for their ancestors, the bacterial periplasmic binding proteins.



The schema represents the GluR5-binding pocket occupied by glutamate (left) and the selective antagonist UBP310 (right). Hydrogen bonds and ion pair sites generated by domains 1 and 2 are colored pink and blue, respectively. The red spheres are water molecules trapped within the binding pocket. See the article by Mayer et al. for details.

▲ Development/Plasticity/Repair

Forming the Deep Cerebellar Nuclei

Andrew J. Fink, Chris Englund, Ray A. M. Daza, Diane Pham, Charmaine Lau, Mary Nivison, Tom Kowalczyk, and Robert F. Hevner

(see pages 3066–3076)

This week, Fink et al. traced the origin of deep cerebellar nuclei (DCN) projection neurons to the rhombic lip, using transcription factors as markers. The DCN cells marched rostrally to the nuclear transitory zone (NTZ) in a subpial stream. Along the way, the cells expressed Pax6, Tbr2, and Tbr1 consecutively, a sequence much like developing neurons of the cerebral cortex. In organotypic cultures, the rhombic lip alone was sufficient to produce this cell population. A subset of the cells expressed reelin, a guidance factor for Purkinje cells, but reelin was not required for DCN migration. Tbr1, however, was instrumental in DCN morphogenesis. Tbr1$^+$ neurons projected to the contralateral DCN, but notably not to the red nucleus. The origin of these glutamatergic neurons in the rhombic lip provides additional support for compartmentalization of cerebellar progenitor cells with GABAergic neurons arising separately from the ventricular zone.

■ Behavioral/Systems/Cognitive

Response Conflicts and the Prefrontal Cortex

Josephine E. Haddon and A. Simon Killcross

(see pages 2933–2940)

Decision making in goal-directed behavior may arise from the prefrontal cortex (PFC), particularly when possible responses conflict with one another. In this week's *Journal*, Haddon and Killcross developed behavioral training and tests as an animal model of these human processes. Rats were trained to respond to each of two audio cues (tones or clicks) and two visual cues (solid or flashing lights) by pressing one of two levers (left or right). The authors provided noticeably different contexts in the form of distinct "wallpapers": checkerboard for audio cues and spotted for visual cues. When conflicting cues eliciting opposite responses were presented together, for example a tone with flashing light, the surrounding context guided rats to the correct response. Except, that is, in rats that received pretraining lesions of the PFC. Lesions of the anterior cingulate cortex at first hindered the contextual disambiguation, but performance in these rats eventually improved.

♦ Neurobiology of Disease

Tottering Inhibition

Sachie Sasaki, Kadrul Huda, Tsuyoshi Inoue, Mariko Miyata, and Keiji Imoto

(see pages 3056–3065)

Aberrant thalamocortical activity underlies human absence epilepsy with its characteristic three per second spike-and-wave EEG activity. *Tottering* (*tg*) mice show a similar epileptic phenotype that results directly or indirectly from a mutation in $Ca_v2.1$ P/Q-type calcium channels. The *tg* mutant channels have reduced calcium influx. Sasaki et al. this week provide evidence that reduction of feedforward inhibition from thalamus to cortex may underlie the absence seizures in *tg* mice. The authors recorded from layer IV cortical pyramidal neurons in brain slices. After thalamic stimulation, feedforward disynaptic inhibition was diminished, as was locally evoked inhibitory (but not excitatory) postsynaptic potentials. The reduction in IPSCs correlated with the developmental onset of absence seizures. The known developmental switch from N-type to P-type ($Ca_v2.1$) at inhibitory synapses in layer IV presumably leads to impaired transmitter release and thus increased cortical excitability in *tottering* mutants.