This Week in The Journal

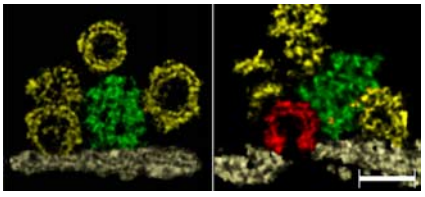
● Cellular/Molecular

Polyhedral Cages Dock Vesicles at Active Zones

Guido A. Zampighi, Nick Fain, Lorenzo M. Zampighi, Francesca Cantele, Salvatore Lanzavecchia, and Ernest M. Wright

(see pages 4151–4160)

When looking at schematic illustrations of proteins found in presynaptic active zones, it is hard to imagine how all those proteins fit together in the cell. Even with electron microscopy, the organization of vesicle docking machinery is difficult to discriminate. But this week, Zampighi et al. present images of active zone complexes that were visualized using conical electron tomography. The authors used semiautomated volume-rendering techniques that colored individual voxels based on density thresholds and/or topology. The resulting images revealed that active zones of rat cortical synapses contain several units, each of which comprised a central polyhedral cage (which the authors call a syndesome) surrounded by synaptic vesicles. Some of these vesicles were partly or fully fused to the plasma membrane, suggesting that the polyhedral cages help mediate vesicle docking and fusion. Interestingly, the polyhedral cages resemble those of clathrin coats, which are normally associated with endocytosis rather than exocytosis.



Reconstructed image of syndesomes (green) and associated vesicles (red and yellow) after semiautomatic sectioning. The red vesicle is fully fused to the plasma membrane. Scale bar, 35 nm. See the article by Zampighi et al. for details.

▲ Development/Plasticity/Repair

Neurturin and Ret Influence Retinal Circuit Formation

Milam A. Brantley Jr, Sanjay Jain, Emily E. Barr, Eugene M. Johnson Jr, and Jeffrey Milbrandt

(see pages 4123–4135)

The receptor tyrosine kinase Ret, which is activated by glial-cell-line-derived neurotrophic factor (GDNF) family ligands (GFLs), is essential for development of many tissues, and GDNF can slow retinal degeneration in animal models. Brantley et al. have detailed the role of this signaling pathway in retinal development. Mice with reduced Ret expression showed decreased light responses, as did mice lacking the GFL neurturin, but not other GFLs. Expression of fluorescent reporters under the control of Ret or neurturin receptor promoters indicated that both of these molecules are expressed in horizontal cells and some amacrine and ganglion cells. In neurturin knock-out mice, the outer plexiform layer (where photoreceptors synapse with horizontal and bipolar cells) was disorganized, horizontal cell axons and dendrites were sparse, bipolar and horizontal cell processes were abnormally long, and synapses were mislocalized to the outer nuclear layer. Therefore, neurturin-mediated Ret signaling appears necessary for normal circuit development in the retina.

■ Behavioral/Systems/Cognitive

Disinhibition Drives OFF Cell Depolarization

Michael B. Manookin, Deborah Langrill Beaudoin, Zachary Raymond Ernst, Leigh J. Flagel, and Jonathan B. Demb

(see pages 4136–4150)

It has been assumed that depolarization of retinal ganglion cells is driven by excitation from bipolar cells. Manookin et al. now report that OFF ganglion cells are also driven by reduced inhibition. Responses to light increments and decrements were recorded in guinea pig ON and OFF ganglion cells. At all increment levels, ON cells received both excitatory and inhibitory inputs; but at each decrement level, increased excitation of OFF cells was paired with decreased inhibition. By sequentially applying receptor agonists and antagonists to test each type of synapse (including gap junctions), it was determined that OFF cell inhibition is mediated by AII amacrine cells, which are electrically coupled to ON cone bipolar cells. When the light dims, ON cone bipolar cells hyperpolarize, which hyperpolarizes AII amacrine cells, thus reducing their inhibition of OFF ganglion cells. This disinhibition is the dominant driving force for OFF ganglion cells when light decrements are small.

♦ Neurobiology of Disease

Microglia Delimit Alzheimer Plaques

Tristan Bolmont, Florent Haiss, Daniel Eicke, Rebecca Radde, Chester A. Mathis, William E. Klunk, Shinichi Kohsaka, Mathias Jucker, and Michael E. Calhoun

(see pages 4283–4292)

Microglia play roles in many neurological diseases, including Alzheimer's disease (AD). In AD, microglia surround amyloid plaques, but it is not clear whether they are harmful (e.g., promoting inflammation) or beneficial (e.g., restricting plaque growth). To gain some insight into their function, Bolmont et al. imaged interactions occurring *in vivo* between microglia and amyloid plaques in a mouse model of AD. Microglia extended and retracted processes in all directions, but those that were near plaques extended more processes toward the plaque. Many nearby microglia migrated to the edge of a given plaque and remained there, but there was an upper limit to the number of microglia surrounding any plaque: larger plaques were associated with larger, not more, microglia. The total volume of microglia surrounding a plaque was predictive of whether the plaque grew over time, and microglia appeared to take up amyloid particles, suggesting the microglia may limit plaque growth.