This Week in The Journal

Cellular/Molecular

N-Terminal Motif Directs Endocytosis of GABA Transporter

Magda S. Santos, C. Kevin Park, Sarah M. Foss, Haiyan Li, and Susan M. Voglmaier

(see pages 10634–10646)

The vesicular GABA transporter (VGAT) loads GABA into synaptic vesicles at presynaptic terminals. When synaptic vesicles are released, VGAT in vesicle membranes ends up in the plasma membrane, from which it must be endocytosed and recycled into new vesicles. Endocytosis of other vesicular neurotransmitter transporters is mediated by adaptor proteins (APs) that interact with dileucine-like motifs in the C-termini of transporters. But VGAT, whose C-terminus faces the vesicle lumen, must use a different endocytosis signal. Santos et al. identified a dileucine-like repeat in the VGAT N-terminus, which faces the cytosol. Mutating residues in this motif nearly abolished endocytosis, so that VGAT was located primarily on the plasma membrane. Such mutations also abolished binding between VGAT and AP-2, which was required for retrieving VGAT from the plasma membrane after vesicle release. Interestingly, mutating a residue upstream of the dileucine-like repeat caused VGAT to associate with AP-3, and this increased the proportion of vesicles in the readily releasable pool, suggesting that APs target vesicles to specific pools.

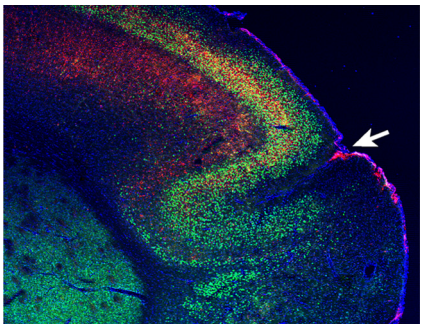
Development/Plasticity/Repair

Fibroblast Growth Factor 2 Induces Gyrification in Mice

Brian G. Rash, Simone Tomasi, H. David Lim, Carol Y. Suh, and Flora M. Vaccarino

(see pages 10802–10814)

Gyrification allows great expansion of the cortical surface without a concomitant disruption of lamination or increase in brain volume. How cortical folding is achieved during development is unclear, but clues can be gathered by inducing gyrus formation in mice, a species that lacks gyri. This has been done by Rash et al. by injecting fibroblast growth factor 2 (FGF2) into the ventricles of embryonic mice during the period of neural progenitor proliferation. FGF2, which promotes progenitor proliferation, induced gyrus and sulcus formation in rostrolateral cortex, where the Sylvian fissure forms in primates, without noticeably altering cortical lamination. Importantly, the number of subventricular zone (SVZ) progenitors and the ratio of SVZ to ventricular zone progenitors increased in rostrolateral areas as gyri began to form, a pattern also seen in regions underlying gyri in gyrencephalic species. In contrast, two other proposed contributors to gyrification—the number of axons and the number of radial glia in the outer SVZ—were similar to controls when gyrification began.



A deep sulcus (arrow) is clearly visible in the cortex of an adult mouse that had received a single intracerebroventricular injection of FGF2 during embryonic development. See the article by Rash et al. for details.

Systems/Circuits

Orientation Selectivity Is Similar in LGN and V1 of Mice

Benjamin Scholl, Andrew Y. Y. Tan, Joseph Corey, and Nicholas J. Priebe

(see pages 10616–10624)

Neurons in primary visual cortex (V1) spike more when a stimulus in their receptive field has the preferred orientation than when stimuli with orthogonal orientations are present. Because orientation selectivity was first discovered in cats, in which relay neurons in the lateral geniculate nucleus (LGN) show little orientation selectivity, this property was hypothesized to arise in V1 neurons by combining inputs from several LGN neurons that respond to spots along a line. Because V1 neurons are orientation selective in all mammals studied thus far, orientation selectivity has been assumed to arise in the same way across species. Recent evidence suggests this is not the case, however. For example, rodent LGN neurons show greater orientation selectivity than cat LGN neurons. In fact, Scholl et al. report that, unlike in cats, the orientation selectivity of mouse LGN neurons is similar to that of subthreshold membrane responses in V1 neurons, suggesting that mouse V1 neurons inherit orientation selectivity from LGN inputs without additional transformation.

Neurobiology of Disease

Increasing Lysosomal Permeability Replicates CLN2 Phenotype

Matthew C. Micsenyi, Jakub Sikora, Gloria Stephney, Kostantin Dobrenis, and Steven U. Walkley

(see pages 10815–10827)

Neuronal ceroid lipofuscinoses are inherited, progressive neurodegenerative diseases involving lysosomal dysfunction and characterized by accumulation of lipid and protein aggregates (lipofuscins) in neurons. The classic late infantile form (CLN2) results from mutations in the lysosomal protease tripeptidyl peptidase 1 (TPP1), and subunit c of mitochondrial ATP synthase (SCMAS), a TPP1 substrate, is a primary component of lipofuscins in CLN2. In healthy cells, when proteins such as SCMAS are dysfunctional, they are tagged with ubiquitin and aggregated by proteins p62 and NBR1, which recruit membrane-associated proteins to construct autophagosomes around the aggregates. Autophagosomes subsequently fuse with lysosomes, in which defective proteins are digested. Micsenyi et al. unexpectedly found cytosolic accumulations of SCMAS, ubiquitin, p62, and NBR1 in neurons of TPP1-deficient mice. These aggregates were not surrounded by membranes, and in fact, lysosomal membranes were disrupted in these neurons. Interestingly, pharmacologically inducing lysosomal membrane permeability (LMP) in wild-type neurons was sufficient to cause aggregation of SCMAS with p62 and NBR1, suggesting LMP occurs in CLN2.