This Week in The Journal

● Cellular/Molecular

G-Protein Modulation of Vesicular Glutamate Transport

Sandra Winter, Irene Brunk, Diego J. Walther, Markus Höltje, Meisheng Jiang, Jens-Uwe Peter, Shigeo Takamori, Reinhard Jahn, Lutz Birnbaumer, and Gudrun Ahnert-Hilger
(see pages 4672–4680)

Neurotransmitter is packed into synaptic vesicles by vesicular transporters. The success of the transporters determines the size of a released "quanta," usually averaging a few thousand molecules. This week, Winter et al. examine regulation of vesicular glutamate transporter (VGLUT) activity by G-protein α subunits. They began by analyzing mice deficient in α subunits. Synaptic vesicles from Gαo2 $^{-/-}$ mice had reduced glutamate uptake and were not affected by an activator of G-proteins, indicating that Gαo2 is exclusively responsible for VGLUT regulation. The glutamate transporters depend on an electrochemical gradient maintained by the proton ATPase. Chloride ions influence the activity of VGLUTs through an interaction between these electrochemical gradient requirements, but chloride ions also appear to have direct effects on transporters. Vesicles from Gαo2 $^{-/-}$ mice lacked chloride activation, suggesting that the G-protein α subunit acts as a direct allosteric modulator. The net effect of activated Gαo2 shifts maximal activity of VGLUTs to lower chloride concentrations.

▲ Development/Plasticity/Repair

Overexpressing Soluble NCAM

Neeta Pillai-Nair, Anitha K. Panicker, Ramona M. Rodriguiz, Kelly L. Gilmore, Galina P. Demyanenko, Josh Z. Huang, William C. Wetsel, and Patricia F. Maness
(see pages 4659–4671)

Neural cell adhesion molecules (NCAMs) exert their influence by homophilic and heterophilic interactions involving their extracellular (EC) domains. The EC domain can be cleaved as a soluble fragment that has the potential to act as a dominant negative, and has been found at elevated levels in brains of schizophrenics. This week Pillai-Nair et al. report on a transgenic mouse with increased expression of the soluble EC fragment in neurons. To avoid effects on development, the authors drove expression with the neuron-specific enolase promoter that is induced late in development and reaches maximum activation in the adult. The mice had reduced GABAergic synapses in frontal cortical areas and in the amgydala, but not in the hippocampus, as determined by several markers for GABAergic nerve terminals. There was also a decrease in synaptophysin immunoreactivity suggesting a decrease in excitatory synapses. The animals showed abnormal behavior, including increased locomotor activity, enhanced responses to amphetamine, and defects in fear conditioning.

■ Behavioral/Systems/Cognitive

Rodent Maternal Deprivation and Morphine Sensitivity

Vincent Vazquez, Jacqueline Penit-Soria, Claudette Durand, Marie Jo Besson, Bruno Giros, and Valérie Daugé
(see pages 4453–4462)

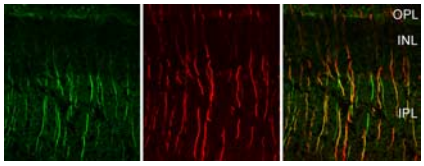
That early maternal separation has behavioral consequences is well known to any parent. However, Vazquez et al. add to the evidence that even short-term maternal deprivation can lead to long-term effects on brain function. Rat pups were isolated from their mother and litter for 3 h per day for the first 2 weeks of life. For rodents, this manipulation is apparently more severe than separating the litter from the mother, perhaps because of a combination of human handling, prolonged isolation, or altered maternal behavior. As adults (2.5–3 months of age), the deprived rats developed a stronger preference for morphine-containing solutions, despite their aversive taste, and spent more time in a morphine-associated chamber. Of note, the enhanced morphine consumption in deprived animals developed gradually over several weeks. In the nucleus accumbens, deprived rats expressed lower levels of preproenkephalin mRNA. The authors suggest that maternal deprivation may increase vulnerability to opioid hypersensitivity and dependence.

♦ Neurobiology of Disease

Endothelin Signaling in Retinal Injury

Amir Rattner and Jeremy Nathans
(see pages 4540–4548)

Photoreceptor degeneration or damage results in activation of Muller cells, the predominant retinal glial cell. This week, Rattner and Nathans report that regardless of cause, whether disease or injury, retinal damage activated a relatively small set of genes. They focused on endothelin2 (EDN2) because it was highly induced after injury and could serve as a signal to Muller cells. As test animals, the authors used *rds* (retinal degeneration slow) and *rd7* (retinal degeneration 7) mutants as well as protocadherin 21 $^{-/-}$ mice, the latter causing slow death of photoreceptors. DNA microarrays, RNA blotting, and *in situ* hybridization revealed a photoreceptor-specific increase in *Edn2* transcripts. Retinas damaged by environmental exposure to visible light and even by retinal detachment responded similarly. In light-exposed mice, transcripts for endothelin receptor B (EDNRB) were also increased in the inner nuclear layer, apparently in Muller cells. The authors suggest that injured or dying photoreceptors send an endothelin2-mediated distress signal to Muller cells.



Endothelin receptor B (green) accumulated in Muller cells labeled with glial fibrillary acidic protein (GFAP; red) in light-damaged retinas. INL, Inner nuclear layer; IPL, inner plexiform layer; OPL, outer plexiform layer. See the article by Rattner and Nathans for details.