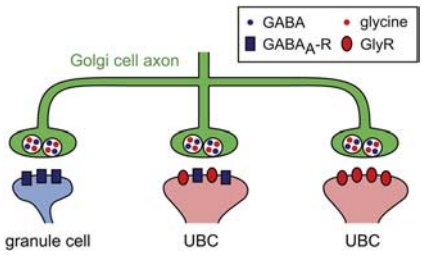
This Week in The Journal

● Cellular/Molecular

Corelease by Golgi Cells Does Not Equal Coresponse

Guillaume P. Dugué, Andréa Dumoulin, Antoine Triller, and Stéphane Dieudonné
(see pages 6490–6498)

Dale's principle, the idea that a neuron releases a single transmitter from all of its terminals, seems to have more exceptions than examples these days. One of the best-studied exceptions is mixed GABA and glycine release from a variety of interneurons, including Golgi cells in the cerebellum. This week, Dugué et al. add a new twist to this story by demonstrating that segregation of receptors at different targets of the same cell can control response specificity. Golgi cells in rat vestibulocerebellar slices generated GABAergic IPSPs onto granule cells but predominantly glycinergic IPSPs onto unipolar brush cells (UBCs). Spontaneous IPSCs in granule cells and UBCs were highly synchronized, indicating that they originated from a common Golgi cell. The GABA-synthesizing enzyme glutamic acid decarboxylase and the glycine transporter GlyT2 colocalized at Golgi cell axon terminals. Thus Golgi neurons apparently corelease two fast inhibitory transmitters, but the postsynaptic receptor expression can dictate the transmitter phenotype.



Model of the postsynaptic selection of cotransmitters by different targets of the Golgi cell. See the article by Dugué et al. for details.

▲ Development/Plasticity/Repair

Rho, Pak3, CREB, and MRX

Jinsong Meng, Yanghong Meng, Amanda Hanna, Christopher Janus, and Zhengping Jia
(see pages 6641–6650)

Mutations in the p21-activated kinase gene *Pak3* are one of the causes of X-linked nonsyndromic mental retardation (MRX). Nonsyndromic simply means that there are no identifiable structural abnormalities in the brain or other organs. This week, Meng et al. examine the possible links between the general cognitive deficits of MRX and signaling by PAK3, which is regulated by the Rho family of GTPases. In wild-type mice, PAK3 was widely expressed in the brain, including the cell bodies and dendrites, but not spines, of hippocampal neurons. Mice deficient for PAK3 had normal brain morphology, but late-phase long-term potentiation was impaired. The levels of phosphorylated cAMP-responsive element-binding protein (pCREB) were also reduced. The knock-out mice were normal in several behavioral tests but showed accelerated extinction of taste aversion memory. The authors suggest that abnormal signaling between Rho, PAK3, and CREB may affect plasticity, and thus could underlie the cognitive deficits in MRX.

■ Behavioral/Systems/Cognitive

Neurons That Keep Us Awake

Maan Gee Lee, Oum K. Hassani, and Barbara E. Jones
(see pages 6716–6720)

The discovery of the role of the orexin (Orx) system in narcolepsy moved this peptide to the head of the class in terms of transmitters and the sleep–wake cycle. Loss of Orx, its receptors, or orexinergic neurons produces narcolepsy in humans and animals, associated with hypersomnolence and sudden onset of rapid eye movement (REM) sleep or paradoxical sleep (PS). To examine the firing patterns of Orx neurons, Lee et al. recorded from perifornical lateral hypothalamic neurons in unanesthetized, head-fixed rats and then labeled the cells with Neurobiotin. Of the 25 recorded and labeled cells, six contained Orx; these fired maximally during active waking. Their discharge rate decreased during quiet waking, and the cells were virtually silent during sleep, including PS. Cells maximally active during slow-wave sleep, PS, or active waking were all Orx negative. Like noradrenergic locus ceruleus neurons, Orx neurons appear to be waking-On and PS-Off cells.

♦ Neurobiology of Disease

Myeloperoxidase and MPTP-Induced Degeneration

Dong-Kug Choi, Subramaniam Pennathur, Celine Perier, Kim Tieu, Peter Teismann, Du-Chu Wu, Vernice Jackson-Lewis, Miquel Vila, Jean-Paul Vonsattel, Jay W. Heinecke, and Serge Przedborski
(see pages 6594–6600)

Ventral midbrain dopaminergic neurons are lost in Parkinson's disease (PD) and after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatment, a neurotoxin that is the standard animal model of this neurodegenerative disorder. This week, Choi et al. show that in both circumstances, myeloperoxidase (MPO) is active and potentially detrimental. Although MPO produces oxidants during inflammation, it was not previously considered to be a contributor to cell damage in PD. MPO mRNA, protein, and enzymatic activity levels rose specifically in the ventral midbrains of mice after MPTP treatment at a time when neuronal loss was greatest. Human PD cases also had elevated MPO in ventral midbrain glial cells. Mice lacking MPO were partially resistant to the structural damage, but not the motor deficits, caused by MPTP. MPO-damaged proteins are distinguished by the modified amino acid 3-chlorotyrosine. This selective biomarker was found in MPTP-treated wild-type animals but not in MPO-deficient mice. Thus MPO may prove to be a therapeutic target in PD.