This Week in The Journal

● Cellular/Molecular

Phosphorylation and Palmitoylation Control PDE10A Localization

Erik I. Charych, Li-Xin Jiang, Frederick Lo, Kelly Sullivan, and Nicholas J. Brandon

(see pages 9027–9037)

Many extracellular signaling molecules, from hormones to neurotransmitters, bind to G-protein-coupled receptors, which activate membrane-associated adenylate or guanylate cyclases and increase levels of cAMP and cGMP. These cyclic nucleotides activate kinases, thus initiating signaling cascades that produce diverse functional effects. Different extracellular signals can produce unique effects via the same cyclic nucleotides because signaling cascades are compartmentalized within the cell. Although cyclic nucleotides are small, diffusible molecules, their effects are spatially and temporally restricted by phosphodiesterases (PDEs), which degrade the molecules at compartmental boundaries. Alternative splicing of multiple genes produces many PDEs with distinct subcellular distributions. For example, PDE10A, a PDE enriched in the striatum, has a cytoplasmic isoform, PDE10A1, and a membrane-enriched isoform, PDE10A2. Phosphorylation of residue Thr16 of PDE10A2 causes its redistribution to the cytoplasm. Charych et al. report that phosphorylation of this site prevents palmitoylation of residue Cys11, which is required for membrane association and transport of PDE10A2 into distal dendrites.

▲ Development/Plasticity/Repair

CXCR2 on Oligodendrocytes Inhibits Remyelination

LiPing Liu, Lindsey Darnall, Taofang Hu, Karen Choi, and Richard M. Ransohoff

(see pages 9074–9083)

Multiple sclerosis (MS) is an autoimmune disease that produces chronic CNS inflammation and demyelination, and may be triggered by environmental toxins or infectious agents. Chemokines and their receptors, which promote migration of leukocytes to sites of inflammation, are thought to be important in MS. Knock-out of the chemokine receptor CXCR2 reduces susceptibility to autoimmunity-induced demyelination in mice, and CXCR2 antagonists decrease lesion size. Although CXCR2 is present on oligodendrocyte precursor cells (OPCs), regulating their migration and proliferation, Liu et al. reported that demyelination in mouse models of MS required CXCR2 expression on neutrophils, but not on OPCs. They now provide evidence that CXCR2 expression on OPCs inhibits remyelination in both autoimmune and toxin models of MS. As shown previously, knock-out of CXCR2 reduced incidence of demyelination. But when demyelination occurred, remyelination was accelerated compared to controls. Whereas introducing CXCR2-expressing neutrophils into knock-out mice facilitated demyelination, they had no effect on remyelination, suggesting that accelerated remyelination resulted from knock-out of CXCR2 on OPCs.

■ Behavioral/Systems/Cognitive

Global Activity of Olfactory Neurons Correlates with Pleasantness

Rafi Haddad, Tali Weiss, Rehan Khan, Boaz Nadler, Nathalie Mandairon, et al.

(see pages 9017–9026)

Although the number of olfactory receptor types is large, the number of discernable odors is much larger, suggesting that most odors are represented by the combined activity of multiple receptors. Based on principal component analysis of data from several studies, Haddad et al. suggest that animals can extract meaningful information from the global population response of olfactory neurons. Regardless of species—fly, rodent, or human—the first two principal components accounted for more than half the variability in responses. In all species, the first component was significantly correlated with the attractiveness of the odor as measured in flies or humans. The second component was correlated with odorant toxicity in rodents. Similar analyses of human descriptions of odors suggested that the first principal component was correlated with pleasantness and the second with toxicity as measured in rats. Thus, across species, the activity of the olfactory neuronal population may represent the pleasantness and edibility of odorants.

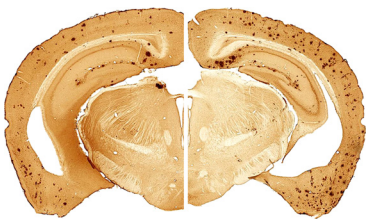
◆ Neurobiology of Disease

Reducing Reelin Exacerbates Alzheimer's Pathology

Samira Kocherhans, Amrita Madhusudan, Jana Doehner, Karin S. Breu, Roger M. Nitsch, et al.

(see pages 9228–9240)

Reelin is a signaling molecule involved in neuronal positioning during development and in learning in adults. In aging animals, reelin accumulates with amyloid precursor protein (APP) fragments in amyloid plaques, and the number of reelin-expressing interneurons decreases with declining cognitive function. Several studies suggest reelin signaling antagonizes the two primary pathological features of Alzheimer's disease (AD), amyloidogenic processing of APP and hyperphosphorylation of tau; and reelin proteolysis appears to be increased in AD. Kocherhans et al. show that reduced reelin expression exacerbates AD-like pathology in mice expressing an AD-associated APP mutation. Amyloid plaques formed sooner, grew larger, and were more numerous in double-transgenic *reln*/*app* mice than in single-transgenic *app* mice. At 15 months, neuronal loss was greater in *reln*/*app* mice, and cortical and hippocampal volumes were reduced. Furthermore, phosphorylation of tau was elevated in double-transgenic mice, and tau accumulated in neurofibrillary tangles in neurons surrounding amyloid plaques, a characteristic of AD that was absent in *app* mice.



Amyloid plaques are larger and more numerous in 15-month-old *reln/app* double-transgenic mice (right) than in *app* single-transgenic mice (left). See the article by Kocherhans et al. for details.