This Week in The Journal

● Cellular/Molecular

Estrogen Reverses Age-Related Increase in Calcium Currents

Lawrence D. Brewer, Amy L. S. Dowling, Meredith A. Curran-Rauhut, Philip W. Landfield, Nada M. Porter, and Eric M. Blalock

(see pages 6058 – 6067)

Calcium is an important regulator of neuronal excitability and plasticity, and altered calcium regulation likely contributes to age-related cognitive decline. L-type voltage-dependent calcium channel (LVCC) currents increase with age, resulting in increased calcium-dependent slow afterhyperpolarization and decreased excitability. Because estrogen influences calcium homeostasis and enhances neuronal excitability and plasticity, loss of estrogen after menopause is also expected to contribute to cognitive decline. Brewer et al. therefore reasoned that estrogen treatment might reverse some effects of aging. In particular, they examined the effects of estrogen replacement on LVCC currents in hippocampal pyramidal neurons of young and old ovariectomized rats. In old rats, estrogen reduced LVCC currents to those of untreated young rats. Although aging alone did not significantly affect expression levels of $Ca_v1.2$ calcium channel mRNA, estrogen decreased levels of $Ca_v1.2$ mRNA, suggesting that estrogen does not reverse the effects of aging, but rather acts by an alternative mechanism to counteract age-related changes.

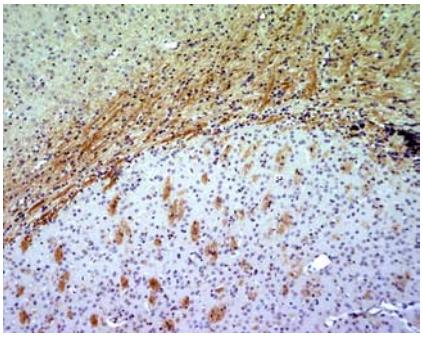
▲ Development/Plasticity/Repair

Differentiation of Oligodendrocyte Precursors Requires mTOR

William A. Tyler, Nitish Gangoli, Pradeepa Gokina, Haesun A. Kim, Matthew Covey, Steven W. Levison, and Teresa L. Wood

(see pages 6367– 6378)

Although named simply for its inhibition by an immunosuppressant drug, the mammalian target of rapamycin (mTOR) has critical functions in all cells: linking extracellular cues such as nutrients and growth factors to cell metabolism, growth, and proliferation, primarily by regulating protein translation. Growth factors activate mTOR indirectly, through the phosphatidylinositol 3-kinase/Akt kinase pathway. Because Akt was recently shown to regulate the differentiation of oligodendrocyte precursor cells (OPCs) into mature myelinating oligodendrocytes, Tyler et al. predicted mTOR would also be important in this process. Differentiation of OPCs into mature oligodendrocytes occurs in a series of steps marked by the expression of specific genes. Analysis of gene expression and cell morphology in rat OPC cultures treated with rapamycin suggested that mTOR normally permits the transition from late OPC to committed immature oligodendrocyte by inhibiting inhibitors of myelin-specific genes. In further support of the hypothesis, mTOR expression increased in parallel with increased myelination *in vivo*.



Immunohistochemistry reveals increased levels of activated mTOR in subcortical white matter of postnatal rat brain during period of increased myelination. See the article by Tyler et al. for details.

■ Behavioral/Systems/Cognitive

FGF Levels Correlate With Anxiety

Javier A. Perez, Sarah M. Clinton, Cortney A. Turner, Stanley J. Watson, and Huda Akil

(see pages 6379 – 6387)

Growth factor deficiency has been hypothesized to predispose people to depression, possibly by decreasing survival of newborn hippocampal neurons. In support of this hypothesis, stimuli that trigger depression reduce, whereas antidepressant treatments increase neurotrophic factor levels and neurogenesis. Furthermore, fibroblast growth factor 2 (FGF2) levels are reduced in depressed humans. To explore links between FGF and mood disorders, Perez et al. examined mice that exhibit inborn differences in anxiety, a trait linked to depression in humans. Rats with a high-anxiety (HA) phenotype had lower levels of FGF mRNA in hippocampus than low-anxiety (LA) rats, and HA rats had more undifferentiated newborn cells and fewer newborn astrocytes in hippocampus. Housing in an enriched environment reduced anxiety-related behaviors and increased hippocampal FGF levels specifically in HA rats. In addition, peripheral FGF administration decreased anxiety-related behaviors in HA rats, and this correlated with increased numbers of newly born neurons and astrocytes in hippocampus.

♦ Neurobiology of Disease

Psychosine Concentrates in Lipid Rafts

Adam B. White, Maria Irene Givogri, Aurora Lopez-Rosas, Hongmei Cao, Richard van Breemen, Gopal Thinakaran, and Ernesto Bongarzone

(see pages 6068 – 6077)

Krabbe disease is a fatal, recessive disorder that appears in infancy and is characterized by a complete loss of myelinating oligodendrocytes and Schwann cells. It is caused by inactivation of galactosylceramidase, a lysosomal enzyme that metabolizes the myelin-specific sphingolipid galactosylceramide. Although the resulting accumulation of unmetabolized galactosylceramide allows macrophages to infiltrate the brain, the main cause of pathology, loss of myelin, is likely caused by accumulation of another, highly toxic sphingolipid, psychosine. Psychosine has no known cellular function, but appears to be synthesized and rapidly degraded during myelination by the same enzymes that synthesize and degrade galactosylceramide. White et al. hypothesized that like other sphingolipids, psychosine might assemble with cholesterol in lipid rafts, and its excessive accumulation might disrupt raft-dependent cell signaling. Indeed, they report that psychosine fractionated with lipid raft molecules in a human patient and in a mouse model of Krabbe disease, and it disrupted the activity of raft-associated protein kinase C.