This Week in The Journal

Cellular/Molecular

Doublecortin Helps Neurofascin Find the AIS

Chan Choo Yap, Max Vakulenko, Kamil Kruczek, Bashir Motamedi, Laura Digilio, et al.

(see pages 7439–7453)

Doublecortin nucleates and stabilizes neuronal microtubules, which are essential for extension of the leading process during migration. Mutations in the microtubule-binding domain of doublecortin greatly impair migration, causing lissencephaly. Doublecortin also binds other proteins, including the cell adhesion molecule neurofascin, but the function of these interactions is essentially unknown. Neurofascin participates in neurite outgrowth early in development, then becomes localized to axon initial segments (AISs) by interacting with AnkyrinG as neurons mature. Yap et al. propose that doublecortin contributes to neurofascin accumulation at the AIS by promoting its endocytosis from other domains. In PC12 cells, coexpressing doublecortin with neurofascin increased neurofascin endocytosis; and in rat hippocampal neurons, knocking down doublecortin or preventing its binding to neurofascin reduced accumulation of newly synthesized neurofascin at the AIS. Previous studies showed that the phosphorylation state of neurofascin determines whether it binds to doublecortin or AnkyrinG, so dephosphorylation might limit neurofascin endocytosis once it arrives at the AIS.

Development/Plasticity/Repair

α7-nAChRs Promote Glutamatergic Synaptogenesis

Adrian F. Lozada, Xulong Wang, Natalia V. Gounko, Kerri A. Massey, Jingjing Duan, et al.

(see pages 7651–7661)

Nicotinic acetylcholine receptors (nAChRs) are widespread in the brain. Early in development, when their expression level is relatively high and glutamatergic synapses are just forming, activation of nAChRs produces spontaneous waves of excitation across large regions of the CNS. Lozada et al. report that activation of these receptors—specifically the subtype composed of α7 subunits—enhances the formation of glutamatergic synapses. Mice lacking α7-nAChRs formed fewer glutamatergic synapses in cortex and hippocampus than wild-type mice, and the deficit remained into adulthood. Furthermore, nicotine increased the number of glutamatergic synapses in dissociated cultures and slices from wild-type mice. Activation of α7-nAChRs was previously shown to accelerate the expression of chloride transporters that cause activation of GABA receptors to hyperpolarize neurons; nevertheless, mice lacking α7-nAChRs produced normal numbers of GABAergic synapses. Therefore, the lack of α7-nAChRs decreased the ratio of excitatory to inhibitory transmission in hippocampus.

Behavioral/Systems/Cognitive

Novelty- and Error-Related Activity Overlap in Frontal Cortex

Jan R. Wessel, Claudia Danielmeier, J. Bruce Morton, and Markus Ullsperger

(see pages 7528–7537)

EEG can be used to identify brain regions involved in processing different types of events. If a person makes an error during a task, a deflection called the error-related negativity (ERN) appears in EEG recordings 50–100 ms later; when an unexpected stimulus is presented, another negative deflection, N2b, appears after 200–300 ms. The peak amplitude of both the ERN and the N2b have been localized to areas of frontocentral cortex in humans, and they have been hypothesized to reflect a role of this area in orienting attention. But because novelty and error are generally studied separately, whether the two EEG signatures arise from the same neuronal population has not been tested directly. Therefore, Wessel et al. used EEG and functional magnetic resonance imaging to identify regions activated in a hybrid error-monitoring/novelty task. The two trial types activated largely overlapping portions of the posterior medial frontal cortex, as well as other cortical and subcortical regions.

Neurobiology of Disease

Phosphatase Expression Level Affects Stress Susceptibility

Chih-Hao Yang, Chiung-Chun Huang, and Kuei-Sen Hsu

(see pages 7550–7562)

Various brain systems regulate physiological responses that enable animals to respond appropriately to stressful events. Ideally, these systems return to basal states after the stressor is gone, but prolonged or traumatic stress can lead to long-lasting, maladaptive psychological states. Individuals differ in their susceptibility to maladaptive effects of stress. For example, Yang et al. found that ~20% of rats exhibited long-lasting deficits in cognitive performance, increased depression-like behaviors, and reduced dendritic spine density in hippocampus after being exposed to inescapable tail shocks. Interestingly, stress-susceptible rats had lower hippocampal expression of the protein tyrosine phosphatase PTPN5 before shocks were administered. Furthermore, knocking down PTPN5 greatly increased the percentage of rats that showed long-lasting effects of stress, whereas overexpressing constitutively active PTPN5 significantly reduced the percentage. Additional experiments suggested that reduced PTPN5 expression increases stress susceptibility partly by enabling excessive upregulation of the voltage-sensitive Ca2+ channel Cav1.2 via prolonged activation of the kinase ERK1/2.