This Week in The Journal

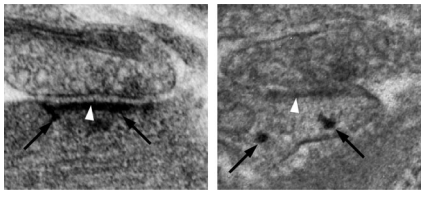
● Cellular/Molecular

SAP97 Isoforms Are Differentially Localized Around Synapses

Clarissa L. Waites, Christian G. Specht, Kai Härtel, Sergio Leal-Ortiz, David Genoux, Dong Li, Renaldo C. Drisdel, Okun Jeyifous, Juliette E. Cheyne, William N. Green, Johanna M. Montgomery, and Craig C. Garner

(see pages 4332–4345)

Regulation of the number of AMPA receptors (AMPARs) at synaptic sites helps determine synaptic strength and contributes to synaptic plasticity. After insertion into the postsynaptic membrane, AMPAR subunits are anchored in the postsynaptic density (PSD) by various scaffolding proteins, which hold receptors adjacent to both presynaptic release sites and downstream signaling molecules. Synapse-associated protein 97 (SAP97) has been implicated in clustering AMPARs at synapses, but contradictory results have led to uncertainties about its function. Waites et al. suggest that some inconsistencies can be explained by differential localization of alternatively spliced SAP97 isoforms. Expression of fluorescently labeled isoforms in cultured hippcampal neurons revealed that αSAP97 was concentrated within the PSD, whereas βSAP97 was primarily localized extrasynaptically. Moreover, although both isoforms increased surface expression of GluR1, only αSAP97 increased the amplitude AMPA-mediated EPSCs. Together, the data suggest that αSAP97 recruits GluR1-containing receptors to the PSD, whereas βSAP97 sequesters them in extrasynaptic regions.



Electron micrographs showing immunogold (black arrows) labeling of synapses. αSAP97 (left) was concentrated at the PSD (white arrowheads), whereas βSAP97 (right) was generally in extrasynaptic regions. See the article by Waites et al. for details.

▲ Development/Plasticity/Repair

Neuroprotective Synaptic Activity Suppresses p53

David Lau and Hilmar Bading

(see pages 4420–4429)

Apoptosis plays an important role during development: eliminating neurons that have not been properly integrated into neural circuits. Later in life, apoptosis eliminates cells that have been damaged by various stressors. Several damaging agents induce expression of the tumor suppressor p53, which triggers apoptosis both by activating transcription of pro-apoptotic genes and by increasing the permeability of the outer mitochondrial membrane to apoptotic factors. The mitochondrial apoptotic pathway is involved in most neurodegenerative diseases. Because synaptic activity can protect neurons from apoptosis, Lau and Bading investigated links between activity and mitochondrial apoptotic pathways. Inducing bursts of action potentials in cultured mouse neurons decreased transcription of the p53 gene and its targets, whereas blocking synaptic activity increased p53-activated transcription, suggesting synaptic activity protects neurons by suppressing p53 activity. In support of this hypothesis, bursting and p53 knockdown similarly reduced loss of mitochondrial membrane integrity induced by excitotoxicity and reduced apoptosis induced by growth factor withdrawal.

■ Behavioral/Systems/Cognitive

Persistent Firing Neurons Function in Trace Conditioning

Sun Jung Bang and Thomas H. Brown

(see pages 4346–4350)

Two methods are commonly used to condition animals to respond fearfully to an otherwise innocuous stimulus: delay conditioning, in which the conditioned stimulus terminates coincidentally with presentation of a noxious unconditioned stimulus, and trace conditioning, in which presentation of the two stimuli are separated by several seconds. Trace conditioning, sometimes used as a model of explicit memory, requires that a neural representation of the conditioned stimulus be maintained until the unconditioned stimulus is presented. Persistent-firing neurons in the perirhinal cortex, which spike for many seconds to minutes after the termination of a stimulus, have been proposed to mediate this function. Persistent spiking of these neurons requires activation of muscarinic acetylcholine receptors (mAChRs). This week, Bang and Brown provide evidence for this hypothesis by showing that injection of an mAChR antagonist into the perirhinal cortex of rats blocked trace conditioning without affecting delay conditioning or contextual fear memory.

♦ Neurobiology of Disease

Endothelial Cells Promote Oligodendrocyte Precursor Proliferation

Ken Arai and Eng H. Lo

(see pages 4351–4355)

Delivery of oxygen and nutrients to active neurons is imperative to brain health. During development, shared growth and guidance molecules coordinate growth and proliferation of neurons, glia, and blood vessels, while in mature nervous systems, interactions between neurons, glia, and vascular endothelial cells regulate blood flow to active regions, as well as maintaining the blood-brain barrier. Recent evidence suggest that endothelial cells also secrete growth factors that promote neuronal proliferation in adults. Arai and Lo now report that factors secreted by endothelial cells also promote proliferation of oligodendrocyte precursors. Culturing oligodendrocyte precursor cells from neonatal rats in the presence of endothelial cells or endothelial-cell-conditioned medium approximately doubled cell mass, both under basal conditions and after exposure of the oligodendrocyte precursors to oxygen–glucose deprivation. The secreted factors mediated this effect by activating Src signaling pathways, which led to phosphorylation of Akt. The endothelial-derived growth factors did not increase differentiation of oligodendrocyte precursors into myelin, however.