This Week in The Journal

● Cellular/Molecular

SAP97 and Dendritic Branching

Weiguo Zhou, Lei Zhang, Xiong Guoxiang, Jelena Mojsilovic-Petrovic, Kogo Takamaya, Rita Sattler, Richard Huganir, and Robert Kalb

(see pages 10220–10233)

Last week we learned that blocking expression of the AMPA receptor GluR1 subunit in motor neurons reduces dendrite growth, leading to impaired motor function. This week, Zhou et al. begin to unravel the molecular mechanisms tying GluR1 to activity-dependent dendritic growth. Intracellularly, glutamate receptors interact with membrane-associated guanylate kinases (MAGUKs)—scaffolding proteins that form the postsynaptic density and anchor signaling and other effector molecules near receptors. GluR1 interacts with the MAGUK synapse-associated protein 97 (SAP97). Overexpression of SAP97 increased dendritic branching, whereas SAP97 knockdown decreased branching in motor neurons. This effect was blocked by an AMPA receptor antagonist. Interaction between GluR1 and SAP97 was required for either to enhance dendritic branching, but only because the interaction localizes SAP97 to the plasma membrane. If SAP97 was targeted to the membrane by the addition of a palmitoylation sequence, its effects on dendritic branching were restored in the absence of direct interaction with GluR1.

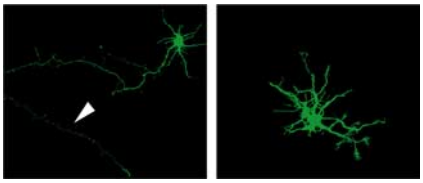
▲ Development/Plasticity/Repair

Endocytosis-Related Proteins in Neuronal Polarity

Ittai Bushlin, Ronald S. Petralia, Fangbai Wu, Asaff Harel, Mohamed R. Mughal, Mark P. Mattson, and Pamela J. Yao

(see pages 10257–10271)

The differential distribution of specific proteins in axons or dendrites underlies the specialized functions of these neurites. At least two mechanisms can create a polarized distribution of centrally produced transmembrane proteins: (1) segregation of proteins into distinct vesicles that are specifically targeted to the appropriate domain, and (2) unsorted transport followed by specific endocytosis of inappropriately expressed proteins. This week, Bushlin et al. suggest that the latter mechanism can be regulated by proteins that associate with endocytic vesicles and determine their cargoes. Knockdown of proteins involved in endocytic vesicle formation, AP180 or clathrin assembly lymphoid myeloid protein (CALM), inhibited axon or dendrite formation, respectively. Knockdown of either protein caused VAMP2—an axonal synaptic vesicle protein that is normally endocytosed from dendrites—to be expressed in all processes, supporting a role in the establishment of polarity. CALM knockdown also reduced surface expression of a secreted protein, suggesting that it may be involved in secretory as well as endocytic pathways.



After 6 d in culture, hippocampal neurons have established several dendrites and a single axon (left, arrowhead). Knockdown of AP180 (right) prevents axon formation. See the article by Bushlin et al. for details.

■ Behavioral/Systems/Cognitive

Security at the Calyx of Held

Myles Mc Laughlin, Marcel van der Heijden, and Philip X. Joris

(see pages 10206–10219)

Large synapses with many active zones are expected to produce large EPSCs and reliably produce action potentials in postsynaptic cells. Therefore, Mc Laughlin et al. were surprised at a recent report that at one of the largest synapses in the mammalian brain—the auditory calyx of Held—presynaptic potentials evoked by auditory stimuli did not reliably produce postsynaptic spikes. The presynaptic calyx has hundreds of active zones, and the synapse is so large that presynaptic and postsynaptic responses can be measured with a single extracellular electrode. Mc Laughlin et al. suspected that prepotentials not associated with a postsynaptic response were actually spikes from nearby axons that did not synapse on the postsynaptic cell. They showed that this was the case by measuring interspike intervals at cat calices. They found that prepotentials associated with a postsynaptic response sometimes occurred within the refractory period of a prepotential that did not produce a response, indicating that they were produced by different neurons.

♦ Neurobiology of Disease

Subtype Specificity of an Allosteric mAChR Agonist

Carrie K. Jones, Ashley E. Brady, Albert A. Davis, Zixiu Xiang, Michael Bubser, Mohammed Noor Tantawy, Alexander S. Kane, Thomas M. Bridges, J. Phillip Kennedy, Stefania R. Bradley, Todd E. Peterson, M. Sib Ansari, Ronald M. Baldwin, Robert M. Kessler, Ariel Y. Deutch, James J. Lah, Allan I. Levey, Craig W. Lindsley, and P. Jeffrey Conn

(see pages 10422–10433)

Five subtypes of muscarinic acetylcholine receptors (mAChRs) are expressed throughout the body, where they exert diverse effects, such as smooth muscle contraction, glandular secretion, thermoregulation, and regulation of behavior, learning, and cognition. mAChRs have been implicated in schizophrenia and Alzheimer's disease (AD), making them attractive as candidate drug targets. Several cholinergic agonists have shown promise for treating these conditions, but most of these drugs bind to the acetylcholine binding site—which is highly conserved across receptor subtypes—and therefore have undesirable side effects. Because of this, drug developers have recently turned to allosteric agonists, which activate receptors by binding to subtype-specific domains outside the acetylcholine binding site. Jones et al. report that one such agonist, which is highly specific for M_1 mAChRs, produced effects in mice similar to effects of atypical antipsychotic drugs, without producing undesirable side effects. Moreover, the drug regulated processing of amyloid precursor protein, suggesting that it may effectively treat AD.