This Week in The Journal

● Cellular/Molecular

Synchronizing Transmitter Release

Tei-ichi Nishiki and George J. Augustine
(see pages 6127–6132)

The molecular calcium sensor responsible for transmitter release has been one of the holy grails of molecular neurobiology. For a number of years, attention has focused on synaptotagmins that have many of the necessary attributes. For example, evoked release is reduced when synaptotagmin I is blocked or eliminated. However, the story is not so simple, because loss of synaptotagmins does not completely eliminate calcium-dependent transmitter release. Evoked transmitter release includes both a fast, synchronous component as well as a slower, asynchronous component. In this issue, Nishiki and Augustine investigated the role of synaptotagmins on transmitter release in mouse hippocampal microisland cultures. They compared the kinetics of EPSCs in synaptotagmin I knock-outs with wild-type neurons. Fast release was lost, but slower, sustained release of transmitter increased. As a result, the total amount of released transmitter was the same in synaptotagmin I knock-outs as in wild type. Thus synaptotagmin I synchronizes fast release while simultaneously reducing slow asynchronous release.

▲ Development/Plasticity/Repair

The Way Traveled from Aβ to Inhibition of LTP

Qinwen Wang, Michael J. Rowan, and Roger Anwyl
(see pages 6049–6056)

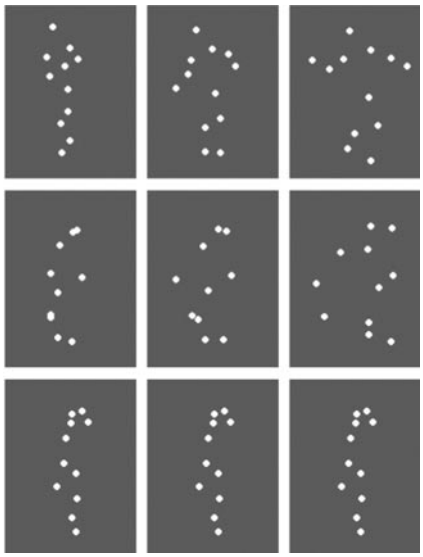
The accumulation of β-amyloid (Aβ) peptide in Alzheimer plaques has led to a number of studies showing that extracellular Aβ can affect synaptic transmission. In this week's *Journal*, Wang et al. examine the signaling cascades involved in Aβ inhibition of NMDA receptor-dependent long-term potentiation (LTP). Their studies point the finger at a cascade involving microglia, inducible nitric oxide synthase (iNOS), and superoxide. They examined iNOS because reactive oxygen species (ROS) are produced by microglia and because plaques are often surrounded by elevated iNOS. Accordingly, iNOS-deficient mice were not susceptible to inhibition of LTP by Aβ. LTP in the presence of superoxide dismutase, a scavenger specific to ROS, and catalase that removes the product hydrogen peroxide, was also resistant to Aβ-mediated inhibition. The authors propose that peroxynitrite, the product of superoxide and nitric oxide, results from plaque activation of microglia and causes oxidation or nitration of a protein required for LTP induction.

■ Behavioral/Systems/Cognitive

A Dozen Points of Light and the Premotor Cortex

Ayse Pinar Saygin, Stephen M. Wilson, Donald J. Hagler Jr, Elizabeth Bates, and Martin I. Sereno
(see pages 6181–6188)

In primates, motor and premotor areas in the frontal lobe are active not only during action production (movement) but also during action perception (observing the movement of friend or foe). Now Saygin et al. test whether frontal lobe activity also occurs in humans watching "point-light motion," in which movement is defined by a dozen or so lights attached to the joints of an actor. The paradigm presents the viewer with cues only about the nature of motion, without other visual information. As a control, frames of the actor's movement were "scrambled," to provide undefined motions. By maximizing fMRI signals, the authors detected frontal lobe activity in response to the points-of-light biological motion. This work suggests that brain areas active in producing movement are also recruited by motion cues alone. The frontal lobe activity may help convert the simple points-of-light image into perceived movement by literally filling in extra dots.



Three frames from a points-of-light animation of an actor throwing an object. The three stimulus conditions were biological motion (top), scrambled motion (middle), and static point-lights (bottom). See the article by Saygin et al. for details.

♦ Neurobiology of Disease

Photoreceptor Calcium and Congenital Blindness

Elena V. Olshevskaya, Peter D. Calvert, Michael L. Woodruff, Igor V. Peshenko, Andrey B. Savchenko, Clint L. Makino, Ye-Shih Ho, Gordon L. Fain, and Alexander M. Dizhoor
(see pages 6078–6085)

In the dark-adapted retina, cyclic nucleotide channels in rods and cones are opened by cGMP, while guanylyl cyclase is held in check by guanylyl cyclase-activating protein 1 (GCAP1), a calcium-binding protein. Light leads to channel closure, a drop in intracellular calcium, unbinding of calcium from GCAP1, and increased guanylyl cyclase activity that replenishes cGMP. Got all that? Well it's important, because GCAP1 has been linked to several forms of human retinal degeneration. This week, Olshevskaya et al. describe the cellular action of a GCAP1 mutation, Y99C, in mutant mice. They report that mutant GCAP has reduced calcium sensitivity, and thus does not completely inhibit cGMP production in the dark, allowing for more channel openings and increased calcium entry. The dynamic rod photoresponse remained intact. However, photoreceptors in the mutant mouse had elevated intracellular calcium and degenerated at a faster rate, commensurate with their expression of the mutant protein. The authors suggest that the disrupted calcium homeostasis contributes to apoptosis.