Learning More About NMDA Receptor Regulation

Anirvan Ghosh

If all the neurotransmitter receptors in the brain, the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor has an unmatched hold on the imagination of neuroscientists. The secret of the NMDA receptor’s enduring appeal is its crucial involvement in regulating changes in the strength of synapses, the regions where neurons communicate. Such changes in synaptic strength (synaptic plasticity) are believed to underlie learning and memory. The NMDA receptor is a multimeric protein complex localized in the membranes of postsynaptic neurons. It consists of an NR1 subunit and one or more NR2 subunits, which form a channel that is permeable to calcium ions. The defining feature of the NMDA receptor is that it allows calcium ions to flow into the postsynaptic neuron when the neurotransmitter glutamate is released into the synapse. An increase in the calcium ion concentration of the postsynaptic neuron triggers a series of biochemical changes that result in modulation of synaptic strength. Despite the fact that the NMDA receptor is a central player in synaptic plasticity, surprisingly little is known about the way in which NMDA receptor–mediated calcium influx is regulated. Reporting on page 491 of this week’s Science (1) and in a recent issue of Neuron (2, 3), the Greenberg, Klein, and Pawson groups shed light on how this NMDA receptor–mediated postsynaptic calcium influx is regulated. Using developing cortical neurons, Takasu et al. (1) show that regulation depends on the Eph receptor tyrosine kinase. Meanwhile, the Neuron papers (2, 3) provide in vivo evidence for the involvement of Eph receptors in synaptic plasticity.

Eph receptors are a large family of receptor tyrosine kinases that regulate various developmental events including cell migration, axon guidance, and regionalization of the nervous system (4). There are two classes of Eph receptors, EphA and EphB, which are selectively activated by ephrinA and ephrinB ligands, respectively. EphrinA ligands are attached to the membrane through a glycosylphosphatidylinositol linkage, and ephrinB ligands are transmembrane proteins. The binding of ephrinB to the EphB receptor is particularly interesting because it leads to tyrosine phosphorylation not only of the receptor, but also of the cytoplasmic domain of the ephrinB ligand itself. Bidirectional signaling through ephrinB ligands and the EphB2 receptor is important for regulating interactions between axons and their cellular targets in the mammalian embryo (4).

The possibility that ephrinB-EphB2 receptor interactions might regulate synaptic strength was first suggested by the observation that EphB receptors are found on postsynaptic membranes (5). Greenberg’s group has shown that ephrinB1 induces the association of EphB2 receptors with the NR1 subunit of NMDA receptors (6). These investigators have also demonstrated that ephrinB1 causes NR1 subunits to cluster at postsynaptic sites. This suggested that the ephrinB1 present in the neuronal membranes of axon terminals might induce the maturation of glutamatergic synapses by promoting aggregation of NMDA receptors in postsynaptic membranes.

Now, Takasu and colleagues (1) extend these observations by revealing that activation of the EphB receptor and its signaling pathway greatly potentiates glutamate-induced calcium influx through the NMDA receptor. In addition, they show that NMDA receptor–induced phosphorylation of the transcription factor CREB and expression of its target genes are also markedly enhanced by EphB2 receptor activation and signaling. Because NMDA receptor–induced calcium influx and altered gene expression are crucial for inducing long-term changes in synaptic strength, regulation of NMDA receptor activity by Eph receptor signaling may influence synaptic plasticity.

Takasu and colleagues also investigated how EphB receptors might modulate NMDA receptor activity. Stimulating cortical neurons with ephrinB2 resulted in tyrosine phosphorylation of the NR2B subunit at three tyrosine residues. They report that ephrinB2-induced potentiation of calcium influx through NMDA receptors, as well as tyrosine phosphorylation of NR2B, requires the cytoplasmic (kinase) domain of the EphB2 receptor. Tyrosine phosphorylation of NR2B appears to be necessary for ephrinB2 to modulate NMDA receptor activity, because a mutant form of NR2B in which the three tyrosine residues cannot be phosphorylated prevents calcium influx in response to EphB signaling.

It appears that the effects of EphB2 signaling on NMDA receptor activity are mediated by a Src family tyrosine kinase. A Src tyrosine kinase called Fyn is known to phosphorylate the NR2B subunit of the NMDA receptor (7). Takasu et al. show that ephrinB2 stimulation of cortical neurons leads to phosphorylation of Src and its association with the EphB2 receptor (see the figure). Also, a dominant negative Src construct (which inhibits multiple Src family kinases) suppresses ephrinB2–induced tyrosine phosphorylation of NR2B and inhibits the potentiation of NMDA receptor–mediated calcium influx. Grunwald et al. (2) also provide evidence for Src activation and tyrosine phosphorylation of a dif-
On Thickening Ice?

Richard B. Alley

The big ice sheets in Greenland and Antarctica are key elements of the global climate system. By storing large volumes of water as ice or ice-contact lakes and sometimes releasing that water abruptly, they can affect sea level, global ocean circulation, and hence Earth's climate, as highlighted on page 476 of this issue by Joughin and Tulaczyk (1).

Modern attention is especially focused on the West Antarctic Ice Sheet (2). Its bed is well below sea level and deepens toward the center. In some models and in reconstructions of the behavior of some past ice sheets, these characteristics are linked to instability. The West Antarctic Ice Sheet has changed greatly since it first formed a few million years ago (3) and has been far from static since humans began observing it a few decades ago (1). Yet in the modern warm period (interglacial), it has long outlasted the melting of most ice-age ice, and circumstantial evidence indicates that the ice sheet persisted through the previous interglacial (4) and probably the two interglacials before that (3).

Predicting the future of the West Antarctic Ice Sheet bears many challenges. Even just measuring the mass balance—whether the ice sheet is growing or shrinking—has proved difficult. One approach is to compare the snow input with the flow output. This requires enough ice-core or other data to determine accumulation rates and enough velocity measurements to capture the ice outflow. Much West Antarctic ice discharges through ice streams with slippery beds. This simplifies the problem as surface and bed velocities are similar, allowing measurements of surface velocities and ice thicknesses to constrain ice outflow.

Early, often heroic efforts to measure mass balance produced important baseline data but left considerable uncertainties because sampling was too sparse to capture the spatial variability. Improvements in ice-core analyses, airborne geophysical surveying, and satellite remote sensing are rapidly reducing these uncertainties and form the basis of the new work by Joughin and Tulaczyk (1). Focusing on the West Antarctic drainage into the Ross Sea, the authors show that on average the ice sheet is thickening slowly.

This new result differs from the best older estimates, which indicated a net thinning for this region (5). Improved data from interferometric synthetic-aperture radar and other techniques contributed to the difference. However, the discharge from this region also has decreased substantially over the last decades as Whillans Ice Stream (formerly called Ice Stream B) slowed near the Ross Ice Shelf (6). Considering the century-old near stoppage of adjacent Ice Stream C (see the figure) (5), it is tempting to identify a trend. Perhaps after 10,000 years of retreat from the ice-age surface and bed velocities are similar, allowing measurements of surface velocities and ice thicknesses to constrain ice outflow.

Early, often heroic efforts to measure mass balance produced important baseline data but left considerable uncertainties because sampling was too sparse to capture the spatial variability. Improvements in ice-core analyses, airborne geophysical surveying, and satellite remote sensing are rapidly reducing these uncertainties and form the basis of the new work by Joughin and Tulaczyk (1). Focusing on the West Antarctic drainage into the Ross Sea, the authors show that on average the ice sheet is thickening slowly.

This new result differs from the best older estimates, which indicated a net thinning for this region (5). Improved data from interferometric synthetic-aperture radar and other techniques contributed to the difference. However, the discharge from this region also has decreased substantially over the last decades as Whillans Ice Stream (formerly called Ice Stream B) slowed near the Ross Ice Shelf (6). Considering the century-old near stoppage of adjacent Ice Stream C (see the figure) (5), it is tempting to identify a trend. Perhaps after 10,000 years of retreat from the ice-age...