This Week in The Journal

Cellular/Molecular

Synaptic and Extrasynaptic NMDARs Activate Different Calpains

Yubin Wang, Victor Briz, Athar Chishti, Xiaoning Bi, and Michel Baudry

(see pages 18880–18892)

Activation of NMDA receptors (NMDARs) leads to Ca^{2+} influx and activation of Ca^{2+}-dependent proteases (calpains). Although calpain activation is neuroprotective in some circumstances, excessive calpain activation is often associated with neuropathology. Because NMDAR activation has opposing effects on neuron viability—synaptic NMDARs promote survival whereas extrasynaptic receptors promote apoptosis—Wang et al. asked whether different calpain isoforms are associated with synaptic and extrasynaptic NMDARs. Indeed, enhancing activation of synaptic NMDARs in cultured cortical neurons increased association of μ-calpain, but not m-calpain, with the NMDAR subunit NR2A and the phosphatase PHLPP1. Activation of synaptic NMDARs reduced levels of PHLPP1, allowing activation of neuroprotective cascades downstream of Akt and ERK kinases, thus increasing neuron survival under stress conditions; all these effects were blocked by selectively inhibiting or knocking down μ-calpain, but not m-calpain. In contrast, activating extrasynaptic NMDARs led to degradation of the phosphatase STEP and increased neuronal death, and these effects were prevented by selectively inhibiting or knocking down m-calpain, but not μ-calpain.

Development/Plasticity/Repair

Membrane Potential Affects Onset of Wallerian Degeneration

Bibhudatta Mishra, Ross Carson, Richard I. Hume, and Catherine A. Collins

(see pages 18728–18739)

After axons are severed, their distal stumps remain intact for hours or even days until an active self-destruction program called Wallerian degeneration sets in, causing stumps to degenerate. Although axonal severing triggers an initial burst of action potentials, the stump subsequently remains silent. Mishra et al. asked whether changes in ion flux after transection contribute to the onset of Wallerian degeneration. Expressing a mutant K^+ channel that reduced resting membrane potential in *Drosophila* motor axons caused the distal stumps to survive twice as long after axotomy as surrounding stumps of wild-type axons. Conversely, expressing a dominant-negative mutant K^+ channel increased excitability and accelerated axonal degeneration. Reducing expression of voltage-gated Na^+ channels also slowed degeneration, but this effect required K^+ channel activity. Mutations that slowed degeneration also slowed Ca^{2+} influx, whereas mutations that accelerated degeneration accelerated Ca^{2+} influx. The authors conclude that changes in K^+ currents change the resting membrane potential and thus increase or decrease influx of Ca^{2+}, which then triggers degeneration.

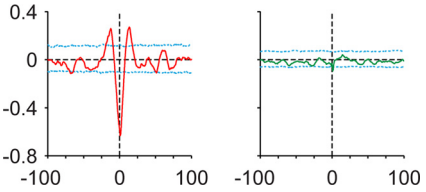
Systems/Circuits

Monosynaptic Connections between L4 and L2/3 Are Sparse

Jianing Yu and David Ferster

(see pages 18855–18866)

Complex cells in layer 2/3 (L2/3) of visual cortex are thought to derive their response properties by integrating inputs from multiple simple cells in L4 of the same column. Electrophysiological recordings have suggested strong, dense, monosynaptic coupling between L4 and L2/3: in ~50% of recorded pairs, L2/3 cells were most likely to spike shortly after L4 cell spikes. Anatomical studies, however, suggest much sparser connectivity. Yu and Ferster reconciled these findings by making paired recordings *in vivo* and calculating the average membrane voltage fluctuation in L2/3 cells triggered off L4 cell spikes. Consistent with previous electrophysiological studies, visually evoked L4 spikes were followed by strong membrane depolarization in L2/3 cells. However, this depolarization generally began slightly before the L4 spike and the amplitude varied. Moreover, coupling usually disappeared when the L4 cell was electrically stimulated. This suggests that what has been interpreted as strong monosynaptic coupling between cell pairs actually reflects simultaneous spiking of numerous L4 cells that converge on L2/3 cells.



An L2/3 complex cell is depolarized when an L4 simple cell in the same column is induced to spike by visual stimulation (left). But when the L4 cell is electrically stimulated, the average membrane potential of the L2/3 cell does not change, indicating the cells are not coupled monosynaptically. See the article by Yu and Ferster for details.

Behavioral/Cognitive

Distraction Improves Memory in Some People

Nathan Cashdollar, Nilli Lavie, and Emrah Duzel

(see pages 19012–19022)

Remembering recent events is more challenging if similar events occur before recall is required. This is particularly true for people with temporal lobe damage. Dissimilar events usually do not affect short-term memory, but Cashdollar et al. show that such events can enhance memory in some people. When healthy subjects viewed images of scenes and were asked shortly afterward whether a particular image had been shown, they performed equally well when an image of a face was presented during the delay and when no image was presented. In people with hippocampal damage, however, presentation of the face improved memory. Magnetoencephalography indicated that coupling of theta-frequency oscillations across frontal areas—which is thought to reflect rehearsal during working memory tasks—decreased during longer delays in healthy subjects who performed well, but remained high in those who performed poorly. Presenting a face during the delay reduced theta coupling and improved performance in the latter subjects, suggesting that distracting stimuli increase accuracy by disrupting rehearsal of faulty memories.