This Week in The Journal

● Cellular/Molecular

Müller Glia Contribute to Neuronal Excitotoxicity

Frédéric Lebrun-Julien, Laure Duplan, Vincent Pernet, Ingrid Osswald, Przemyslaw Sapieha, Philippe Bourgeois, Kathleen Dickson, Derek Bowie, Philip A. Barker, and Adriana Di Polo

(see pages 5536–5545)

Glaucoma and vascular occlusion are thought to kill retinal neurons by glutamate-induced excitotoxicity. Excitotoxicity is generally thought to result from excessive activation of neuronal NMDA receptors, massive calcium influx, and subsequent activation of apoptotic pathways; but preventing excitotoxicity with NMDA receptor antagonists in clinical settings has been problematic, suggesting targeting other pathways may be beneficial. Lebrun-Julien et al. provide evidence that activation of NMDA receptors on retinal glia leads to release of tumor necrosis factor α (TNFα), which causes upregulation of calcium-permanent AMPA receptors in neurons, and this contributes to excitotoxicity. NMDA increased expression of the nuclear transcription factor NF-κB and its transcriptional target TNFα in mouse retinal Müller glia *in vivo*. Blocking NF-κB activity reduced NMDA-triggered cell death as effectively as blocking NMDA receptors, whereas inhibiting TNFα or calcium-permanent AMPA receptors reduced, but did not eliminate NMDA-induced neuronal death. Therefore, glial NF-κB may activate transcription of other genes that further contribute to neuronal death.

▲ Development/Plasticity/Repair

Re-Expression of α9 Integrin Promotes Axon Regeneration

Melissa Andrews, Stefan Czvitkovich, Elisa Dassie, Tineke Vogelaar, Andreas Faissner, Bas Blits, Fred H. Gage, Charles ffrench-Constant, and James Fawcett

(see pages 5546–5557)

Nerve regeneration in adult animals is prevented by the developmental downregulation of growth-related proteins in axons and the upregulation of growth-inhibitory factors in lesioned areas. For example, the extracellular matrix protein tenascin-C is present in glial scars and one subunit of its receptor, α9 integrin, is not expressed in adult neurons. Andrews et al. reasoned that re-introduction of α9 integrin would permit axonal growth on tenascin-rich substrates. Indeed, virus-mediated expression of α9 in dorsal root ganglion (DRG) neurons in culture increased axon outgrowth on tenascin-C. Promisingly, expression of α9 in DRG and spinal cord neurons *in vivo* increased axonal growth into lesioned areas, although the growth was not as extensive as axonal growth *in vitro*. Furthermore, although α9 expression enabled recovery of thermosensation, it did not restore mechanosensation. Nonetheless, the results suggest that re-introduction of developmentally downregulated proteins, in conjunction with other treatments, could improve functional recovery after nerve injury.

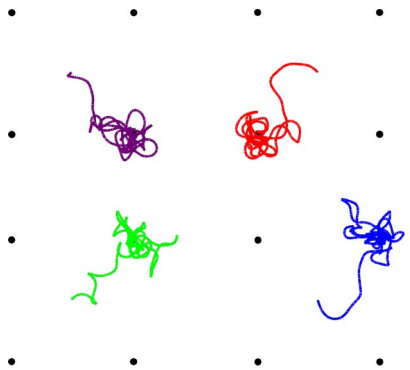
■ Behavioral/Systems/Cognitive

Nematodes Use Two Chemotaxic Strategies

Yuichi Iino and Kazushi Yoshida

(see pages 5370–5380)

In nonuniform environments, nematodes move toward higher concentrations of nutrients. For many years, the only behavioral strategy shown to produce this chemotaxis was the pirouette, in which, when encountering decreasing concentrations of nutrient, worms briefly reverse direction, make a sharp bend, and move forward in a new, somewhat random direction. Computer simulations showed that this behavior successfully steers worms toward nutrient sources; but simulated worms did not perform as well as real worms. Iino and Yoshida now describe a second chemotaxic strategy used by nematodes: the weathervane, in which worms gradually turn toward higher nutrient concentrations. Worms generally pirouetted when nutrient concentration was decreasing along their path of movement, whereas they weathervaned when the concentration gradient was perpendicular to their path. Together these two strategies can account for the performance of real worms. Although neuron ablations identified some neurons required for chemotaxis, neurons specific for either of the two strategies remain to be found.



Computer models of nematodes that use weathervane and pirouette chemotaxic strategies navigate to nutrient sources as well as real worms. See the article by Iino and Yoshida for details.

♦ Neurobiology of Disease

Blocking ASIC1a Reduces Depressive Behaviors in Mice

Matthew W. Coryell, Amanda M. Wunsch, Jill M. Haenfler, Jason E. Allen, Mikael Schnizler, Adam E. Ziemann, Melloni N. Cook, Jonathan P. Dunning, Margaret P. Price, Jon D. Rainier, Zhuqing Liu, Alan R. Light, Douglas R. Langbehn, and John A. Wemmie

(see pages 5381–5388)

Stress can lead to depression in humans; in mice, stress produces behaviors reminiscent of human depression, such as reduced seeking of pleasant stimuli and reduced avoidance of unpleasant conditions. Although the extent to which the physiological underpinnings of depression-like behaviors in mice overlap with those underlying depression in humans, antidepressants attenuate them, and they are therefore useful for identifying new potential mechanisms and treatments. Coryell et al. report that knocking out the acid-sensing ion channel ASIC1a attenuated stress-induced reduction in sugar-water consumption and decreased immobility in tail-suspension and forced-swim tests. Antidepressants targeting serotonin, dopamine, and norepinephrine further reduced immobility in knock-out mice, suggesting that ASIC1a effects are partially independent of these other systems. Nonetheless, like other antidepressants, ASIC1a knock-out prevented stress-induced reductions in hippocampal levels of brain-derived neurotrophic factor. The results suggest that ASIC1a inhibitors may reduce depression in people who are not successfully treated with current treatments.