This Week in The Journal

Cellular/Molecular

Driving Purkinje Cells with Resurgent Sodium Current
The Contribution of Resurgent Sodium Current to High-Frequency Firing in Purkinje Neurons: An Experimental and Modeling Study
Zayd M. Khaliq, Nathan W. Gouwens, and Indira M. Raman
(see pages 4899–4912)

In the classic view, tetrodotoxin-sensitive sodium channels generate the upstroke of the action potential and then rapidly, and rather completely, inactivate. Other aspects of action potential shape and the firing pattern of individual neurons have usually been attributed to various potassium channels or other ion channels operable at subthreshold membrane potentials. However, it turns out that the sodium channels are more complex than this simple model. This is nicely illustrated by the Nav1.6 subunit that is absent in ataxic med mutant mice. Nav1.6 is perhaps best known as the major sodium channel isoform at mature nodes of Ranvier, but it is also one of the three sodium channel isoforms at axon initial segments. Nav1.6 channels have a curious biophysical property: they reactivate quickly as the action potential repolarizes (so-called “resurgent current”). The resurgent current can increase excitability in the subthreshold voltage range. Khaliq et al. examined the influence of Nav1.6 on Purkinje cell firing patterns using med mice. Isolated Purkinje cells from these mice showed less spontaneous firing, a lower firing rate, and modestly smaller sodium currents. Using simulations of the ion channels in Purkinje cells, Khaliq et al. conclude that resurgent current, at least for these cells, has a dominant role in promoting spontaneous activity and increasing action potential generation.

Development/Plasticity/Repair

Engrailed-1 in the Background
Factors in the Genetic Background Suppress the Engrailed-1 Cerebellar Phenotype
Natalie A. Bilovocky, Rita R. Romitodifiacomo, Crystal L. Murcia, Stephen M. Maricich, and Karl Herrup
(see pages 5105–5112)

The influence of genetic background on behavioral phenotypes is well recognized. In fact, this can be used to look for genes underlying specific phenotypes. In this issue, Bilovocky et al. provide a particularly dramatic example of the influence of genetic background on brain development. They examined the mouse homeodomain gene Engrailed-1 (En1) that is expressed during early development at the midbrain/hindbrain (MHB) junction. Mutant mice lacking En1 have abnormal MHB development, with virtual absence of the cerebellum. However, Bilovocky et al. report that the En1+/− phenotype is nearly completely suppressed on a C57BL/6J genetic background. What happened? The authors note that the background change from 129/Sv to C57BL/6J does not affect the Engrailed-2 mutant phenotype. Although En1 and En2 are thought to be interchangeable in the CNS, En2 is expressed later in development, and En2 mutants have a much milder phenotype. The authors suggest that in C57BL/6J mice, En2 can compensate for En1, at least for the cerebellum. Consistent with this idea, the mutant phenotype reappeared when En1+/− C57BL/6J mice were also En2+/−.

Behavioral/Systems/Cognitive

Modeling Cellular Timers in Prefrontal Cortex
Self-Organizing Neural Integrator Predicts Interval Times through Climbing Activity
Daniel Durstewitz
(see pages 5342–5353)

Predicting events before they occur is among the most sophisticated capabilities of the bird and mammalian brain. Even more remarkably, the time of occurrence can be anticipated based on incoming sensory information. This ability allows us to take in information from a constantly changing environment and to make decisions about our reactions and behavior. “Executive” functions such as prediction, planning, and timing involve the prefrontal cortex. However, the cellular mechanisms for time prediction are not well understood. One candidate mechanism is “climbing activity,” the gradual increase in sustained activity in prefrontal neurons during the delay between cue and choice options in working memory tasks. This week, Durstewitz presents a single-cell biophysical model that is sufficient to produce climbing activity via an intrinsic positive feedback loop based on firing rate, the resulting Ca2+ flux, and other Ca2+-activated inward currents. The author suggests that the activity could be self-organizing if the neurons “learn” to use variations in intracellular Ca2+ concentration to finely tune the feedback loop. The model provides specific mechanisms by which neurons might work as biological timers capable of representing a time span that ranges from hundreds of milliseconds to tens of seconds. The model also passes a critical test: it makes several predictions that are experimentally testable.