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 operative 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 α subunits expressed in Purkinje cells, and the major one at the axon initial segment. 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.

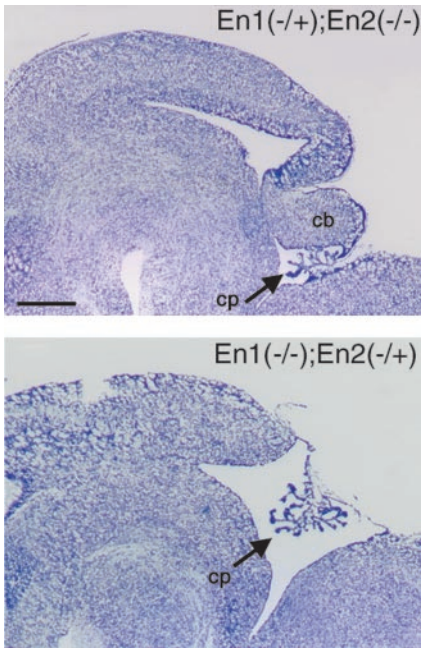
▲ Development/Plasticity/Repair

Engrailed-1 in the Background

Factors in the Genetic Background Suppress the *Engrailed-1* Cerebellar Phenotype

Natalie A. Bilovocky, Rita R. Romito-DiGiacomo, 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 from129/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 $En2^{+/-}$.



The cerebellum is present in $En1^{-/+}/En2^{-/-}$ mice (top, cb) but is absent in $En1^{-/-}/En2^{-/+}$ mice (bottom), as shown in sagittal sections from embryonic day 17.5. This image is taken from Figure 7 of this article.

■ 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 Ca^{2+} flux, and other Ca^{2+}-activated inward currents. The author suggests that the activity could be self-organizing if the neurons "learn" to use variations in intracellular Ca^{2+} 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.