NEUROLOGICAL DISORDERS

Keeping pace with ataxia

File name:

NRN0406_KN_HL

Word count:

Accompanying
picture:

File name of picture:

URLs

Episodic ataxia type 2 (EA2) is a rare form of inherited ataxia, characterized by attacks of incoordination and migraines. This disorder is caused by mutations in the P/Q type of voltage-gated calcium channel, which is widely expressed in presynaptic terminals of many neurons. These channels are especially abundant in the Purkinje neurons of the cerebellum, a brain area known to be crucial for motor coordination. Writing in *Nature Neuroscience*, Walter and co-workers now provide an explanation for how P/Q channel deficits cause irregular firing of Purkinje neurons, and how this, in turn, leads to ataxia.

Under normal circumstances, Purkinje cells spontaneously fire continuously (at rates of ~40 Hz). This pacemaking activity is regulated mainly by small (SK) and large (BK) conductance calcium-activated potassium channels. P/Q channels activated during an action potential recruit SK channels, which stay active between spikes. This, in turn, generates a conductance that contributes to the hyperpolarization of the membrane potential between action potentials; recruitment of the depolarizing channels that drive the next spike requires these well-timed

hyperpolarizations.

These researchers took advantage of rodent models of EA2 known as leaner, tottering and ducky. Each of these mouse strains has an ataxic phenotype due to mutations in the P/Q channel gene. Using recordings from cerebellar slices, they found that in both ducky and leaner mice, the precision of the intrinsic pacemaking of the Purkinje cells was reduced without affecting the mean firing rate of Purkinje cells. They also found that the erratic pacemaking of Purkinje cells in these mutant mice reduced the accuracy of the Purkinje cells in encoding and transmitting the synaptic information they receive from the cerebellar cortex to neurons of the deep cerebellar nuclei.

To prove that the irregular firing of Purkinje neurons causes an ataxic phenotype, the authors used 1-ethyl-2-benzimidazolinone (EBIO), a drug that increases the affinity of SK channels for calcium. This drug did not alter the firing pattern of wild-type neurons, but made the mutant neurons fire more regularly. Chronic perfusion of EBIO into the cerebella of ducky and tottering mice improved their performance on an accelerating motor rod (a standard test for motor

coordination) and reduced both the frequency and severity of dyskinetic attacks that these mice experienced. Importantly, EBIO did not affect wild-type mice.

These findings not only provide a mechanistic explanation for how mutations in P/Q channels can cause ataxia, but also identify a new target for future therapeutic approaches for EA2. There are some differences between the mouse models of EA2 and human patients with EA2 — the patients have other non-cerebellar symptoms, such as muscle weakness, and we do not yet know if human patients suffer from irregular Purkinje cell firing. Whether EBIO or other SK channel modulators will work their magic in human patients remains to be seen, but Walter *et al.* have provided the blueprint for future studies on this topic.

Kalyani Narasimhan, Senior Editor
Nature Neuroscience

ORIGINAL RESEARCH PAPER Walter, J. T. *et al.* Decreases in the precision of Purkinje cell pacemaking cause cerebellar dysfunction and ataxia. *Nature Neurosci.* **9**, 389–397 (2006)

FURTHER READING Otis, T. S. & Jen, J. C. Blessed are the pacemakers. *Nature Neurosci.* **9**, 297–298 (2006)