channels was affected by the seizures. In the epileptic animals, transcription of the KV4.2-channel gene was downregulated, and the activity of many of the remaining channels was decreased through protein kinase C-mediated phosphorylation.

Many studies have implicated inherited ion-channel defects in epilepsy, and this study illustrates that channelopathies can also be acquired as a result of seizure activity. If similar phenomena are shown to underlie seizure facilitation in humans, new anti-epileptic drug targets might be identified on the basis of the molecular mechanisms that modulate dendritic excitability.

Heather Wood

References and links

ORIGINAL RESEARCH PAPER Bernard, C. *et al.* Acquired dendritic channelopathy in temporal lobe epilepsy. *Science* **305**, 532–535 (2004)

FURTHER READING Staley, K. Epileptic neurons go wireless. *Science* **305**, 482–483 (2004) | Steinlein, O. K. Genetic mechanisms that underlie epilepsy. *Nature Rev. Neurosci.* **5**, 400–408 (2004)

WEB SITE

Encyclopedia of Life Sciences:
http://www.els.net/
epilepsy

NEUROLOGICAL DISORDERS

A new role for *spastin*

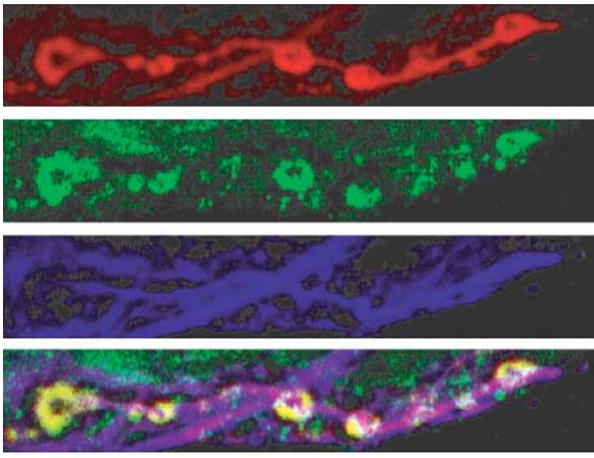
Hereditary spastic paraplegia is a devastating motor disorder that causes spastic weakness of the lower limbs and eventual axonal degeneration. More than 40% of all cases are associated with mutations in one gene, *spastin*, but little is known about how such mutations cause the disease. Reporting in *Current Biology*, Trotta *et al.* found that *spastin* mutations might lead to defects in neurotransmission by affecting microtubule functions.

Spastin is an ATPase that contains a microtubule-interacting domain. Therefore, the authors asked whether microtubule structure or function might be affected by abnormal *spastin* expression. They studied this in the *Drosophila melanogaster* neuromuscular junction (NMJ) synapse, which has been widely used to assay functions of the microtubule cytoskeleton and to model its role in inherited neurological diseases.

Spastin is expressed at high levels in the nervous system of both mammals and *D. melanogaster*, but its subcellular localization has not been characterised. Trotta *et al.* found that the protein is highly enriched in axons and synaptic connections. They showed that spastin co-localizes with a synaptic vesicle protein, synaptotagmin, indicating that spastin is expressed in the synaptic vesicle pool domain of the presynaptic bouton.

The authors showed that knockdown of ubiquitous *spastin* expression by RNA interference causes lethality. When they knocked down *spastin* expression specifically in the nervous system, the animals had very poor coordination and locomotor abilities. Interestingly, overexpression of *spastin*, either ubiquitously or specifically in the nervous system, was also lethal to embryos or early larvae. The authors suggest that a correct dose of *spastin* expression is crucial for normal development.

Spastin interacts with microtubules and prevents their assembly *in vitro*. The authors assessed the effects of altered *spastin* expression *in vivo* on microtubule assembly and synaptic transmission. They found that, at the NMJ presynaptic terminal, *spastin* knockdown in the neuron led to an accumulation of acetylated α-tubulin, the post-translationally modified form of tubulin that occurs only in structurally stable microtubules. Conversely, neuron-specific overexpression of *spastin* caused a reduction in stabilized tubulin and, often, the stabilized tubulin network was no longer detectable.



Confocal micrograph of a *Drosophila melanogaster* neuromuscular junction. Signals represent immunoreactivity for different antibodies. Red, anti-horseradish peroxidase labelling neuronal membranes; green, anti-D-spastin; blue, anti-acetylated tubulin, which detects stable and long-lived microtubule filaments. Note that regions where D-spastin is enriched also appear to be regions where stable microtubules are excluded. Image courtesy of K. Broadie, Vanderbilt University, USA.

The authors showed that these effects on microtubule assembly correlated with changes in synaptic transmission. When they stimulated the motor nerve and measured glutamate-gated synaptic currents in the voltage-clamped muscle, they found that loss of *spastin* expression resulted in an increase in current amplitude, whereas *spastin* overexpression had the opposite effect. These effects could be reversed by pharmacological agents that affect microtubule stability. Normal functions were restored in *spastin* knockdown flies by nocodazole, which disassembles microtubules, and in flies overexpressing *spastin* by taxol, which stabilizes tubulin monomers. In both cases synaptic transmission was indistinguishable from that in normal animals.

The study shows that *spastin* is enriched at the synapse and controls synaptic transmission by regulating microtubule assembly. Trotta *et al.* conclude that it is likely that defects in microtubule stability are the primary cause of hereditary spastic paraplegia. This mechanistic insight has significant implications in designing therapeutic strategies to treat the illness.

Jane Qiu

References and links

ORIGINAL RESEARCH PAPER Trotta, N. *et al.* The hereditary spastic paraplegia gene, *spastin*, regulates microtubule stability to modulate synaptic structure and function. *Curr. Biol.* **14**, 1135–1147 (2004)

FURTHER READING

Reid, E. Science in motion: common molecular pathological themes emerge in the hereditary spastic paraplegias. *J. Med. Genet.* **40**, 81–86 (2003)