Investigating the genetics of seizure-prone flies

Researchers have identified the basic cellular mechanism that causes epilepsy-like seizures in *prickle* mutant flies (*Drosophila melanogaster*). The study identifies a novel pathway in the pathophysiology of epilepsy.

In multiple species, including flies, mice, zebrafish and humans, mutations in orthologs of the *prickle* gene result in epileptic phenotypes. Seizure-prone *prickle* mutant flies show behavioral defects (such as uncoordinated gait) and electrophysiological defects (problems in the electrical properties of biological cells) that are similar to other fly models of seizure disorders. Little is known about the cellular process that leads to these phenotypes, however.

J. Robert Manak (University of Iowa, Iowa City) led a study to answer this question. To determine whether mutations in *prickle* were solely responsible for the seizure phenotype in flies, Manak's team studied flies in which the balance between two isoforms of the *prickle* gene in neurons was altered: one group was partly deficient in the pk^{sple} isoform, and one group was partly deficient in the pk^{pk} isoform. After subjecting the

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flies to a behavioral assay in which they were mechanically stimulated with a vortex mixer for 20 s, they assessed the flies' recovery time. Flies in which the pk^{pk} isoform predominated had longer recovery times, and they also showed increased susceptibility to seizures induced by electroconvulsive stimulation (*Proc. Natl. Acad. Sci. USA* doi:10.1073/pnas.1403357111; published online 14 July 2014).

Products of *prickle* work in conjunction with a group of cytoplasmic and membrane-associated proteins that must be properly transported within vesicles in order for normal communication between neurons to occur. To determine how *prickle* isoforms may modify the transport of these important proteins to cause seizures, the researchers assessed the movement of vesicles along axons in *D. melanogaster* larvae. Both groups of flies with altered levels of *prickle* isoforms showed impaired vesicle transport, demonstrating that the balance between *prickle* isoforms is important for normal vesicle transport in axons of fly neurons. Overall, when the balance was tipped towards pk^{pk} isoforms, anterograde vesicle movement was enhanced, altering axon polarity and leading to seizures. Consistent with this finding, seizures were suppressed when vesicle transport was impeded by reducing expression of two motor proteins responsible for the movement of vesicles along axons.

Interestingly, the pathway implicated in underlying seizures in this study has previously been associated with neurodegenerative diseases. The study may lead to further associations between the cellular dynamics underlying epilepsy and those underlying neurodegenerative disorders such as Alzheimer's disease.

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NEGATIVE PRESSURE LIMITS TRAUMATIC BRAIN DAMAGE

Traumatic brain injury (TBI) carries a high risk of death or disability, owing in part to a lack of treatment options. In previous studies, Louis Argenta (Wake Forest University Health Sciences, Winston-Salem, NC) and colleagues found that controlled application of negative pressure to localized areas of TBI in rats promoted healing and improved outcomes. With those results in mind, they sought to refine some parameters of their technique, which they call mechanical tissue resuscitation (MTR), and to evaluate its safety and efficacy in a large-animal model that more closely resembles TBI in humans.

The researchers tested the MTR approach by inducing localized TBI in swine and then applying negative pressure over the injured area (*Neurosurgery* **75**, 152–162; 2014). They evaluated the effects of different levels of pressure (–50 or –100 mmHg), different treatment periods (3 or 5 days) and different delay times (no delay, 3 hours or 6 hours) on the size of the damaged area, the volume of hemorrhage and the appearance of the damaged tissue.

The results showed that MTR after TBI improved outcomes in swine. The procedure seemed to be safe: none of the treated pigs developed seizures or brain deformation. Brain tissue of treated animals had a more normal appearance by magnetic resonance imaging and by histological examination than did tissue of untreated animals. Application of –100 mmHg of pressure for 3 days resulted in significantly smaller damaged areas and less bleeding compared with application of no pressure or of –50 mmHg of pressure. All the animals that were treated by MTR for 5 days after injury survived, whereas half of animals that were treated for only 3 days died when treatment was stopped. Delaying treatment by 3 hours did not diminish its efficacy, but delaying treatment by 6 hours resulted in less benefit.

Argenta's group concludes that "[t]he ability of mechanical tissue resuscitation to achieve meaningful reduction in loss of brain tissue and hemorrhage injury warrants further investigation." Additional studies are needed to optimize the MTR technique and to address aspects of the technique such as clinical feasibility and management of infection risk before initiating clinical trials in humans with TBI. But the results in swine suggest that MTR holds promise for the treatment of TBI, perhaps in combination with pharmacological approaches. The researchers believe that the technique may also have a role in treating other conditions that involve brain hemorrhage, such as subdural hematoma, stroke and brain tumor resection.

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