CURRENT LITERATURE

EPILEPSY RESEARCH TAKES FLIGHT

Genetic Suppression of Seizure Susceptibility in *Drosophila*

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PURPOSE: Despite the frequency of seizure disorders in the human population, the genetic and physiologic basis for these defects has been difficult to resolve. Although many genetic defects that cause seizure susceptibility have been identified, the defects involve disparate biologic processes, many of which are not neural specific. The large number and heterogeneous nature of the genes involved make it difficult to understand the complex factors underlying the etiology of seizure disorders. Examining the effect known genetic mutations have on seizure susceptibility is one approach that may prove fruitful. This approach may be helpful both in understanding how different physiologic processes affect seizure susceptibility and in identifying novel therapeutic treatments.

METHODS: In this study, we have taken advantage of *Drosophila*, a genetically tractable system, to identify factors that suppress seizure susceptibility. Of particular interest has been a group of *Drosophila* mutants, the bang-sensitive (BS) mutants, which are much more susceptible to seizures than are wild type. The BS phenotypic class includes at least eight genes, including three examined in this study, *bss, eas,* and *sda*. Through the generation of double-mutant combinations with other well-characterized *Drosophila* mutants, the BS mutants are particularly useful for identifying genetic factors that suppress susceptibility to seizures.

RESULTS: We found that mutants affecting Na^+ channels, mle^{napts} and *para*, K^+ channels, *Sh*, and electrical synapses, *shak-B*^{2}, can suppress seizures in the BS mutants. This is the first demonstration that these types of mutations can suppress the development of seizures in any organism. Reduced neuronal excitability may contribute to seizure suppression. The best suppressor, mle^{napts}, causes an increased stimulation threshold for the giant fiber (GF), consistent with a reduction in single-neuron excitability that could underlie suppression of seizures. For some other double mutants with *para* and Sh^{KS133}, there are no GF threshold changes, but reduced excitability also may be indicated by a reduction in GF following frequency.

CONCLUSIONS: These results demonstrate the utility of *Drosophila* as a model system for studying seizure susceptibility and identify physiologic processes that modify seizure susceptibility.

COMMENTARY

Advances in molecular biology have led to the discovery of a variety of gene mutations that can render an individual (or rodent) seizure susceptible. Identification of these seizure-susceptibility genes involved inactivation of specific gene products in mice or detailed genetic mapping in humans. Both strategies are time consuming and limited to uncovering gene mutations that increase brain excitability, resulting in a predisposition to the development of an epileptic phenotype. Genetic factors also can result in seizure suppression, but it has proven difficult to explore this possibility in great detail.

Now identification of seizure-suppressing gene mutations is experimentally feasible. Kuebler et al. developed a novel strategy that takes advantage of the fruitfly *Drosophila*, a genetically tractable and widely used model organism. Initially, in a series of electrophysiologic studies, the authors demonstrated that high frequency (HF) stimulation of the giant fiber (GF) pathway evokes epileptiform-like afterdischarges in wild-type flies. This electrical activity, recorded from DLM indirect flight muscles, represents a generalized seizure discharge in the fly and is followed by a period of synaptic failure. Interestingly, a group of *Drosophila* excitability mutants called "bang-sensitive" (BS mutants) are 5 to 10 times more susceptible to seizure activity after HF stimulation. In this study, the authors crossed BS seizure-susceptible mutants with previously identified *Drosophila* mutants exhibiting sodium channel (*para,* mle^{napts}), potassium channel (*eag, slo,* Sh^{KS133}), or gap junction (*shak-B*^{2}) deficits. Double-mutants were then tested by using the HF stimulation protocol, and it was determined that genetic background can

dramatically influence seizure susceptibility. For example, the seizure threshold for *sda* flies is ~2 V, but when these mutants are crossed with a voltage-gated Na^+ channel mutant (*para*), their seizure threshold is increased to wild-type levels (*para; sda* ~39 V). Although seizure susceptibility in BS mutants could be suppressed with all double-mutant combinations tested, a range of suppression was observed in these experiments suggesting that factors influencing seizure generation are complex.

Novel strategies such as this have the potential to advance greatly our understanding of the pathogenesis of seizures. Moreover, this study should encourage greater use of genetically tractable model organisms, such as *Drosophila, Danio rerio,* and *Caenorhabditis elegans*, in epilepsy research.

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