

Commentary

Fever, molecular excitability and epilepsy

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The transmission of the electrical impulse across neuronal membranes relies on innumerable excitable molecules that visit an array of conformations. It is not surprising, then, that the best recognized manifestation of cerebral hyperexcitability, a seizure, should exhibit some temperature dependence. From an enzyme catalysis perspective, a brief temperature increase from, say, 37 to 39 °C, exerts only a modest influence on the overall progress of most reactions. Nevertheless, when the body temperature increases in this fashion, some individuals – estimated at a few percent of all children – become very prone to seize. How neurons become hyperexcited to cause even a simple, self-limited seizure remains largely unmeasured. It is known, however, that, at rest, already over one-half of the cerebral energy is spent by the Na⁺-K⁺-ATPase on restoring dissipative ionic gradients [5] and that, during a seizure, the cerebral metabolic rate increases threefold [4]. If one considers that the transmission of just a photon through the retina results in the hydrolysis of 7000 ATP molecules [2], it is possible to begin to imagine the energetic cost of a seizure, especially when it is compounded by fever and consumption of ATP precursors. Few biological processes consume as much energy as a febrile seizure while retaining reversibility; hence the interest on the molecular cause of this type of epilepsy. Several seizure susceptibility genes are known because, at first, many neuronal ion channels intuitively became the subject of intense scrutiny. Discovery, however, progressed slowly, and some investigators have relegated febrile epilepsy to the gray realm of polygenic, multifactorial diseases. Yet, others believe that there are several diseases mistakenly simplified as one syndrome of febrile seizures and that this complicates gene isolation. This may all be true, but newer evidence has revealed the unexpected

protagonism of non-ion channel – and even of extraneuronal – molecules in genetic epilepsy. In both old and new epileptic phenotypes, inexcitable-protein genes such as the G-protein-coupled receptor fragment VLGR1 gene *MASSI* [6], the soluble protein gene *LGII* [1], and, now, the casein kinase $\gamma 2$ gene *CSNK1G2* [3], are receiving close attention, while three other loci associated with febrile epilepsy are also under investigation. After all, a great deal of excitability takes place in the backstage of the synapse and even outside of the neuron.

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