Epileptic Sodium Channelopathy

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Epilepsy is a neural disease that characteristically involves seizures induced by supranormal excitation of nerve cells, with a high incidence of 1% of the total population. Epilepsy includes many types, a majority of which are assumed to be associated with genetic causes. Multiple causal genes for epilepsy have, in fact, been identified. Mutations of genes encoding the voltage-dependent sodium-channel alpha subunits (SCN1A, SCN2A, SCN1B) have been reported in patients with epilepsies. Especially in SCN1A, more than 200 disease mutations have been found in wide variable types of epilepsy of differing degrees of severity. It is now well established that SCN1A is the most representative causal gene for epilepsy. Severe myoclonic epilepsy in infancy (SMEI), one of the types of epilepsy where mutations in SCN1A have been found, is characterized by febrile seizures as the initial symptom in infancy, intractable tonic-clonic seizures and myoclonic seizures, and mental development disorders. Mutations are found in a surprising 80% of cases. About two-thirds of such mutations are nonsense or frameshift mutations that introduce premature terminations into the channel protein; and about one-third are missense mutations. We produced mice possessing SCN1A with a nonsense mutation found in three independent SMEI cases. It was found that the mice with mutations introduced lost the Nav1.1 protein encoded by SCN1A, developed epilepsy, and had inhibitory nerve cell dysfunction. Furthermore, from strictly designed and implemented experiments using multiple antibodies and the mutant mouse as a negative control, it was found that wild mice had Nav1.1 protein expression in particular (parvalbumin-positive) inhibitory nerve cells where a calcium-binding protein called parvalbumin was expressed, and the Nav1.1 expression was especially predominant in their axons. The Nav1.1 protein has traditionally been thought to express itself in the dendrites and somas of both excitatory and inhibitory nerve cells. Our discovery, however, that the expression of the protein is localized to the axons of parvalbumin-positive inhibitory nerve cells, etc., disproves this assumption found in prior relevant reports, and it furthermore strongly suggests that the cause of development of epilepsy of the types induced by SCN1A gene mutations, such as SMEI, resides in the weakened functions of parvalbumin-positive cells failing to inhibit the activities of excitatory nerve cells. There is high expectation that a means of developing new therapies for severe, debilitating epileptic diseases that are difficult to cure at present will be found by targeting parvalbumin-positive inhibitory nerve cells.

References

