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REVIEW

The relevance of individual genetic background and its role in animal models of epilepsy

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Summary Growing evidence has indicated that genetic factors contribute to the etiology of seizure disorders. Most epilepsies are multifactorial, involving a combination of additive and epistatic genetic variables. However, the genetic factors underlying epilepsy have remained unclear, partially due to epilepsy being a clinically and genetically heterogeneous syndrome. Similar to the human situation, genetic background also plays an important role in modulating both seizure susceptibility and its neuropathological consequences in animal models of epilepsy, which has too often been ignored or not been paid enough attention to in published studies. Genetic homogeneity within inbred strains and their general amenability to genetic manipulation have made them an ideal resource for dissecting the physiological function(s) of individual genes. However, the inbreeding that makes inbred mice so useful also results in genetic divergence between them. This genetic divergence is often unaccounted for but may be a confounding factor when comparing studies that have utilized distinct inbred strains. The purpose of this review is to discuss the effects of genetic background strain on epilepsy phenotypes of mice, to remind researchers that the background genetics of a knockout strain can have a profound influence on any observed phenotype, and outline the means by which to overcome potential genetic background effects in experimental models of epilepsy.

Contents

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Introduction

Epilepsy is one of the most prevalent neurological disorders affecting people of all ages (Chang and Lowenstein, 2003; Meldrum, 1992). Although epilepsy affects between 1 and 3% of the population and many cases are familial, only a few epilepsy genes have been mapped; likely due to the genetic complexities that underlie the most common epilepsies (Gurnett and Hedera, 2007; Ottman, 1997; Scheffer and Berkovic, 2003). Moreover, the heterogeneity of the epilepsies, epileptic seizures, and differences in individual patient susceptibility render the identification of genetic loci responsible for differential susceptibility to both seizures and its consequences challenging in humans. Although the importance of genetic factors in determining susceptibility to seizure induction and its neuropathological consequences is generally accepted, the specific genes responsible for this susceptibility are largely unknown.

Most traits and diseases are genetically complex, resulting from combinations of several genes or from interactions between genetic and environmental factors (Lander and Schork, 1994; Moore and Nagle, 2000). Epileptic disorders are no exception to this rule in that they are quantitative traits, resulting from variation in multiple genes with small to moderate effect (reviewed in Rees, 2010; Steinlein, 2010). Inter-individual variation in epilepsy susceptibility suggests that some subpopulations are at increased risk to the detrimental effects of seizures, and it has become clear that genetic background is an important susceptibility factor.

Mouse models offer an attractive strategy for investigating complex neurological disorders, such as epilepsy. The majority of genetic studies, especially those involving disease, have employed mice, not only because their genomes are so similar to that of humans, but also because of their availability, ease of handling, high reproductive rates, and availability of extensive sequence data for inbred strains (http://www.informatics.jax.org/). In addition, inbred mouse strains demonstrate significant strain differences (i.e. genetic heterogeneity) in susceptibility to a variety of seizure induction agents as well as the consequences of seizures, thus providing a starting point for dissecting genetic influences involved in modulating complex traits in humans. Similar to the complexity observed in humans, the determinants of this differential susceptibility in murine populations are probably multigenic, and still remain to be determined. Thus, the opportunity to study discrete epilepsy mutations on a diverse choice of strain backgrounds, to develop better models, and identify the impact of genetic modifiers on seizure severity, incidence and its consequences is now available. This review aims to update on the issue of genetic background as a potential confound in studies of epilepsy and to discuss genetic factors contributing to variance in results from different laboratories.

Mouse models of epilepsy: genetic heterogeneity

Rodent models of chronic epilepsy based on chemoconvulsant-induced status epilepticus capture many of the key features of acquired human epilepsy. Animals injected with chemoconvulsants, such as kainic acid or pilocarpine, undergo repetitive limbic seizures and status epilepticus for several hours followed by a variable latent period, lasting between days and several weeks, preceding a chronic phase characterized by spontaneous seizure activity (Hellier et al., 1998; Leite et al., 2002). In particular, many of the features of the neuropathology of medically intractable temporal lobe epilepsy in human tissue, such as neuronal loss and sprouting of recurrent axons (Babb et al., 1991; De Lanerolle et al., 1998; Houser et al., 1990; Mathern et al., 1995) are similar to those changes found in rodents subjected to status epilepticus induced by systemic kainic acid or pilocarpine (Ben-Ari, 1985; Buckmaster and Dudek, 1997; Gorter et al., 2001; McNamara et al., 1992; Turski et al., 1983; Williams et al., 2004).

However, while inbred mouse strains have played a critical role in biomedical research due to their genetic homogeneity *within* inbred strains, genetic divergence *between* inbred mouse strains can serve as a confounding factor when comparing studies that have utilized different inbred strains. In particular, even in the absence of engineered mutations, different inbred strains can vary drastically in their susceptibility to clinically relevant diseases.

For example, susceptibility to chemically or electrically induced seizures has been studied extensively in genotypic and phenotypic diverse mouse strains (Ferraro et al., 1995; Frankel et al., 2001; Kosobud and Crabbe, 1990; McKhann