Phenotypic and Genetic Variations in C57BL/6J and DBA/2J Mice Using the Flurothyl Model of Epileptogenesis

by

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ABSTRACT

The C57BL/6J strain of mice has been shown to undergo a kindling phenomenon, in which upon repeated daily exposure to the seizure-inducing chemoconvulsant, flurothyl, the amount of time it takes to have a generalized seizure decreases (Samoriski and Applegate, 1997; Ferland and Applegate 1998a). During this kindling effect, the seizures are contained in the forebrain seizure circuitry and are characterized by clonic movements of the face and/or hindlimbs and forelimbs. Following this induction phase of flurothyl exposure and a 28-day rest period, flurothyl rechallenge results in an alteration in the behavioral seizure phenotype expressed. The seizure now is expressed via the brainstem seizure circuitry, which can be described as a wild running seizure with hopping sometimes followed by tonic extension solely of the forelimbs or in combination with the hindlimbs (Samoriski and Applegate, 1997; Ferland and Applegate 1998a). That is, during the induction phase the seizure is almost always clonic and of the forebrain seizure circuitry whereas after the rest period and upon flurothyl rechallenge, the seizure is tonic and of the brainstem seizure circuitry. Several different strains of inbred strains of mice are known to have differences in seizure characteristics. In this study, we were interested in how some of these mouse strains behaved in the flurothyl kindling model. We tested several inbred strains of mice A/J, 129S1, and DBA/2J in addition to C57BL/6J mice using this flurothyl paradigm. Our data showed significant differences 1) in day 1 seizure latency in the induction phase, 2) in the kindling effect, and 3) in the behavioral seizures phenotypes observed upon flurothyl rechallenge. The A/J strain of mice did not exhibit the typical loss of posture used to classify the start of a forebrain-clonic seizure making this strain of mice difficult to study. The 129S1 mice were unique in that they had lethal brainstem seizures during the induction phase and thus could not be used in this study, since they were not able to complete the entire kindling paradigm. As compared to C57BL/6J, the DBA/2J mice had a lower seizure threshold on day 1, did not demonstrate the kindling effect, and did not have an alteration in seizure phenotype upon flurothyl rechallenge. We then tested DBA/2J and C57BL/6J F1 hybrid mice and determined that the F1 hybrid mice had a higher initial seizure threshold on trial 1 of the induction phase similar to C57BL/6J, a kindling effect similar to C57BL/6J mice, but did not undergo the alteration in behavioral phenotype as

seen in DBA/2J mice. These data demonstrate the significance of the genetic background of these strains of mice as it relates to seizure susceptibility and/or resistance. Our future work will take advantage of the genetic differences in these strains of mice in order to try to identify genes that may be responsible for these seizure traits. Using chromosome substitution strains, in which a single chromosome from a donor mouse is transferred to a host mouse, we can use these strains of mice to isolate quantitative trait loci in hopes of finding the underlying genetic cause of these phenotypic changes.