Preliminary Behavioral, Biochemical and Neuropathological Characterization of a New Epilepsy Mutant (Poster)

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INTRODUCTION

Epilepsy is a common heterogeneous neurological disease characterized by spontaneous seizure phenomena and a number of associated behavioral and co-morbidities. Numerous antiepilepsy drugs and other alternative therapies are available to treat patients with epilepsy, however, up to 30% of patients do not obtain satisfactory results. The best approach for understanding the risk for development and progression of epilepsy is to study patients with specific genetic alterations in these seizure mice. Future directions of this work should take into consideration genetic mapping and wide analysis of single nucleotide polymorphisms that may help to shed light on structural and functional differences between model and control mice.

METHODS

Western Blot Analysis

Western blot assay to measure ROBO1 in brain frontal cortex from naïve FVB/NJ male and female mice. The ROBO1 protein is a non-receptor tyrosine kinase, which plays a key role in the development and function of the neuronal guidance system. The protein is expressed in the developing brain and is required for the proper guidance of axons to their target. The Western blot assay was performed using standard protocols, including protein extraction, denaturation, and electrophoresis. The blots were probed with a primary antibody specific to ROBO1 and visualized using a secondary antibody conjugated with an enzyme. The intensity of the bands was quantified using densitometry software.

RESULTS

Western Blot Analysis

Figure 1. Western Blot assay to measure ROBO1 in brain frontal cortex from naïve FVB/NJ male and female mice. The ROBO1 protein is a non-receptor tyrosine kinase, which plays a key role in the development and function of the neuronal guidance system. The protein is expressed in the developing brain and is required for the proper guidance of axons to their target. The Western blot assay was performed using standard protocols, including protein extraction, denaturation, and electrophoresis. The blots were probed with a primary antibody specific to ROBO1 and visualized using a secondary antibody conjugated with an enzyme. The intensity of the bands was quantified using densitometry software.

Figure 2. Time line of a representative spontaneous behavioral seizure expressed by male 191 on the onset of spontaneous seizures. The seizure threshold was measured using an electroshock test. The time line shows the sequence of events leading to the onset of a spontaneous behavioral seizure in a mouse. The seizure was characterized by loss of posture and tonic extension of the limbs. The seizure was also associated with a decrease in locomotor activity and a change in the respiratory rate. The electroshock threshold was measured using a ramped current (dc), and the threshold was found to be lower in the seizure mouse compared to the control mouse.

Figure 3. Maximal electroshock seizure threshold (MEST) in F1 and parental (B) OR15155 mice. We tested the hypothesis that the putative seizure-mutation(s) lowers MEST, and that this effect can be detected prior to the onset of spontaneous seizures. MEST was measured using a computerized electroshock test (method: daily shock via ear electrodes and step-wise current increase) when mice were 6-9 months of age, at a time when no mouse had observed to have spontaneous seizures. Both females (N=16) and males (N=11) were studied. A statistically significant gender difference was documented (P<0.01 Student's t-test). Several outliers were deleted (A). Measurement of MEST in several older parental OR15155 mice (-12-18 months of age) revealed a lower range of values compared to the younger F1 mice (B) for both genders. The females with the lowest MEST and the 2 males with the lowest MEST are known to express spontaneous seizures.