OMICS Group Conferences
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International Conference and Exhibition on
Neurology & Therapeutics

May 14-16, 2012 Embassy Suites Las Vegas, USA

Transcriptome profiling of hippocampal CA1 after early life seizure-induced preconditioning may elucidate new genetic therapies for Epilepsy

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The molecular biology underlying resistance of the immature brain to seizure-induced injury remains unknown. Previously, we showed that injury of the CA1 but not CA3 subregion induced by a single injection of kainic acid (1xKA) is attenuated when juvenile animals (P20) have a history of two sustained neonatal seizures on P6 and P9 (3xKA). To identify gene candidates involved in the spatially protective effects caused by multiple early life seizures we profiled and compared the transcriptomes of the isolated CA1 subregion from juvenile rats injected with PBS, 1xKA or 3xKA. Out of 9834 genes quantified 7.1% were differentially expressed following 1xKA and 9.6% following 3xKA. Significant transcriptional changes were observed in the following gene categories: oxidative stress response, cellular growth and development, inflammation, and alterations in glutamatergic and GABAergic neurotransmission. The repeated induction of seizures (3xKA) was found to target the same gene categories, however, the responses were enhanced and largely consisted of cell protective mechanisms. For example multiple seizures strongly increased expression of Bcl-2 family members and related adaptor proteins associated with anti-apoptotic pathways. Furthermore, distinct interleukins such as anti-inflammatory cytokines (IL6 transducer, IL23 and IL33) and their receptors (ILF2) that are usually not observed in adult tissues were significantly up-regulated. Gene-specific quantitative PCR (QPCR) produced results consistent with those observations. Expression of pro-apoptotic effector casp-6 for example, was increased after 1xKA but reduced by 50% following 3xKA. Similarly, expression of pro-inflammatory cox1 was unchanged after 1xKA but significantly reduced by ~70% after 3xKA. Ca^{2+} imaging studies in the rat hippocampus revealed enhanced N-methyl-D-aspartate (NMDA) responses following 1xKA but attenuated currents after 3xKA. Thus, the observed differential transcriptional and functional responses may contribute to early life seizure-induced pre-conditioning and neuroprotection via reduced hippocampal Ca2+ permeability and the redirection of inflammatory and apoptotic pathways. The current status of this work clearly encourages a closer look at new gene-based therapies to treat epilepsy.

Biography

Dr. Friedman earned her Ph.D at the age of 28 years from Mount Sinai School of Medicine. She is an Associate Professor at the New York College of Osteopathic Medicine of New York Institute of Technology. She has published more than 35 papers in high-impact journals and serves as an editorial board member for the journal Amino Acids. Furthermore, she serves on the abstract and program committee of the Epilepsy Society, and she is an active member of the Society for Neuroscience since 1985 and the Epilepsy Society since 1991.

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