AUTOIMMUNE EPILEPSY: GLUTAMATE RECEPTOR ANTIBODIES ARE FOUND IN EPILEPSY PATIENTS, ACTIVATE GLUTAMATE RECEPTORS, AND CAUSE COGNITIVE ABNORMALITIES AND BRAIN DAMAGE IN ANIMAL MODELS

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About 50 million people worldwide have epilepsy (with almost 90% of these people in developing countries). In fact, 1-2% of the world population suffers from over 40 different types of epilepsy, each type presents with its own unique combination of seizure type, typical age of onset, EEG findings, treatment, and prognosis.

The etiology of the epilepsy is often unknown. Furthermore, 20-30% of epilepsy patients do not benefit from any anticonvulsant medication. Such patients may suffer from multiple seizures per day and from numerous neurological and behavioral problems among them attention-deficit/hyperactivity disorder (ADHD), mood disorders such as depression and anxiety, and abnormal learning and memory, which together make their life miserable.

For decades, epilepsy is considered a brain disorder caused ONLY by various neurological factors. Breaking this dogma, it is now asked: Can specific **autoimmune responses** - i.e. deleterious immune responses against self proteins/antigens - contribute to the .initiation and/or the worsening of some epilepsies, and also be associated with neuropsychiatric and cognitive dysfunction in some epilepsy patients? If so, current treatment of such patients, which completely ignores autoimmune etiology, should take this into consideration and should be modified to include suppression of the detrimental autoimmune responses.

In a series of studies over the last ~ 10 years, we found that antibodies (Abs) to ionotropic-glutamate-receptor-subtype-3 peptide B (GluR3B) are found in ~35% of patients with different types of epilepsy. In addition, GluR3B Abs can: 1) activate their autoantigen (i.e., the receptor, GluR3) in neurons; 2) induce ion currents; 3) kill neurons and cause brain pathology in vivo. Furthermore, in a recent study (paper in preparation), we postulated that GluR3B Abs lower the threshold of seizure initiation by inducing neurotoxicity, and contribute to neurobehavioral impairments, such as those frequently seen in epilepsy patients. Testing in a preliminary study whether these GluR3 Abs are more frequent among 21 epilepsy patients exhibiting neurobehavioral impairments, we found tantalizing results: 19/21 (90%) of the GluR3B Ab-positive epilepsy patients had learning problems, 16 (76%) had attention problems and 15 (71%) had psychiatric problems. In sharp contrast: only 4 (20%) GluR3B Ab-negative patients (n=20) had learning disabilities, and none had psychiatric problems.

We further found in an animal model that DBA/2J mice immunized with GluR3B and expressing high levels of specific GluR3B Abs were significantly more susceptible to PTZ-induced seizures than GluR3B Ab-negative mice, manifested by a greater overall seizure severity score, and higher percentage of mice developing generalized seizures. Furthermore, a significant correlation was observed between the levels of GluR3B Abs and the seizure score. The GluR3B Ab-positive mice also exhibited abnormal neurological behavior, significantly different from the GluR3B Ab-negative mice, in three different behavioral tests: they were less active and more anxious in the open-field, stayed for shorter times on a Rota-rod, and fell more in the Grip test (paper in preparation),.

Together, our recent findings indicate that anti-GluR3B Abs may indeed contribute to higher susceptibility of developing epilepsy, and to neurobehavioral impairments, such as those exhibited by some epilepsy patients. On this basis, we recommend to diagnose and to attempt to silence glutamate-receptor Abs in some human neurological diseases in which glutamate receptor Ab's are found, especially in intractable epilepsy, as they may genuinely contribute to the overall neuropathology.

In future studies on 'Autoimmune Epilepsy', we wish to: 1) deepen and extend our previous studies and look for possible autoimmune-mediated neuropsychiatric and cognitive impairments in patients with intractable seizures, as well as in those with new onset epilepsy; 2) carry out a genetic investigation of these patients, in order to establish a possible correlation between autoimmunity to GluR3B and specific human leukocyte antigen (HLA) haplotypes; 3) Treat patients found positive for GluR3B Abs and neuropsychiatric abnormalities with IVIg, to be administered repetitively over ~1 year, with the aim to control their autoimmune responses and ameliorate the pathology.

As a whole, the data we already have in hand, and our planned studies, may pave the way to the elucidation of a novel etiology in some types of epilepsy, i.e., Ab's to glutamate receptors, and of their impact on neurobehavioral and cognitive abnormalities that often accompany the seizures themselves. Moreover, it may result in a modified treatment so as to include suppression of the autoimmune responses in order to treat both the symptoms of epilepsy and the neurobehavioral deficits.