Autoimmune epilepsy

MIA LEVITE

The Sackler Faculty of Medicine, Tel Aviv University and The Weizmann Institute of Science, Rehovot, Israel. (mia.levite@weizmann.ac.il)

An estimated 0.5–1% of the world population is epileptic, some with completely unknown etiology and no effective treatment. Epilepsies have long been viewed as diseases of the central nervous system (CNS), but in recent years, evidence has mounted that some may actually be autoimmune-mediated. If so, the way we regard and treat these epilepsies may require a revolutionary change. A session—which was sponsored by The Avraham and Sonia Rochlin Foundation—dealing, for the first time, with the "autoimmune epilepsy" concept took place in February 2002 at the International Congress of Autoimmunity in Geneva, Switzerland. Some salient findings reported at this session are relayed here.

The first clue to the autoimmune nature of some epilepsies came from the presence of antibodies to a major excitatory neurotransmitter in the CNS. Antibodies to this particular glutamate receptor, one of the AMPA (α-3-hydroxy-5-methyl-4-isoxazolepropionic acid) subtypes (GluR3), have now been found in three severe human epilepsies: Rasmussen's encephalitis (RE), noninflammatory focal epilepsy and "catastrophic" epilepsy (C. Antozzi & R. Montezzega, Italy). Specific cleavage of GluR3 by granzyme B, a serine protease released by activated immune cells, generates the GluR3B autoantigenic peptide, but only when an internal NH_2-linked glycosylation sequence within the GluR3 recognition-sequence is not glycosylated (S. Rogers' group, USA). Interestingly, $CD3^+CD8^+$ cytotoxic T cells that contain granzyme B can be found in close association with neurons in the brains of RE patients and could contribute to neuronal death (H. Lassman's group, Austria).

Like glutamate, some antibodies to GluR3B activate neurons, but *via* amino acids 372–386, which are distant from the glutamate binding site. This is the first example of an autoantibody that is able to activate a neurotransmitter receptor and open its ion channel. Immunoreactivity towards GluR3B Phe^{380} was suggested as an index for agonist and excitotoxic neurocidal potential (S. Rogers' group). These autoantibodies kill through more than one mechanism. An excitotoxic mechanism, *via* overactivation of the glutamate receptors, leads to neuronal death, similar to that caused by excess glutamate in various pathological conditions (S. Rogers; M. Levite, Israel; A. Basile, USA). A complement-dependent mechanism, at a different time-scale, also kills both neurons and astrocytes. (J. McNamara, USA).

Some crucial factors may influence whether autoimmune epilepsy develops. Antibodies in the periphery that are specific for GluR3 may have restricted access to the CNS and hence to the autoantigen (J. McNamara & M. Levite). Also, the cytokine milieu (primarily IFN-γ and TNF-α) may further dictate whether autoimmune epilepsy would develop (Y. Ganor & M. Levite).

Epileptic RE patients harbor a kaleidoscope of non-GluR3 antibodies, although surgical removal of the epileptic loci only reduces the concentration of antibodies to GluR3B in the serum and cerebrospinal fluid (CSF), pointing to their special relevance (Y. Ganor & M. Levite). Antibodies against Munc-18, a presynaptic intracellular protein required for neurotransmitter release, are also suggested to be especially relevant (J. McNamara). Finally, a proportion of patients with seizures, cognitive changes and sleep disorders (limbic syndromes) or epilepsy associated with Hashimoto's or viral encephalitis harbor autoantibodies against voltage-gated potassium channels (A. Vincent & B. Lang, UK).

What initiates epilepsy? Viral or bacterial infections of RE patients before the presence of symptoms may contribute to the disease. A direct causal link between viral infection and the production of excitotoxic antibodies to GluR3 was demonstrated by the immunization of mice with LP-BM5 murine leukemia virus, which evoked (by partial molecular mimicry) antibodies to GluR3 that were able to activate and kill neurons *via* excitotoxicity (A. Basile). Immunogenetic factors may contribute to susceptibility. Preliminary evidence was presented concerning a group of eight adult RE patients that showed a significantly increased frequency of HLA-A2 (100% of patients; 24% of controls), HLA-B44 (67% of patients; 5% of controls) and HLA-DR4 (83% of patients; 36% of controls) (I. Hart, UK) and from some pediatric RE patients with either HLA-A2 or HLA-B44 (Y. Ganor & M. Levite). In mice, the amount of antibodies to GluR3B also depends on their major histocompatibility background (M. Levite).

Functional hemispherectomy—a surgical intervention that disconnects the epileptic areas by removing certain cortical structures—is so far the only recommended therapy for RE patients that are unresponsive to anticonvulsants. Novel and striking support for beneficial immunotherapy of RE was presented at the meeting. After long-term treatments with monthly hIVIg (intravenous human immunoglobulin, 2 g/kg) and an H2 antagonist (histamine receptor 2 antagonist), all eight treated adult RE patients showed significant improvements in function, decreased seizures, SPECT (single photon emission computed tomography), MRI (magnetic resonance imaging) and less inflammation in the CSF. These improvements were maintained for up to 5 years (I. Hart). In addition, selective removal of IgG by protein A immunoadsorption was effective in one RE patient who had detectable antibodies to GluR3; removal caused interruption of status epilepticus on different occasions, reduced seizure frequency and improvement of cognitive functions (C. Antozzi). Finally, plasma exchange or IVIg evoked good responses of patients with epilepsy-associated Hashimoto's or viral encephalitis (B. Lang), in which antibodies to voltage-gated potassium channels were found.

Together, the above findings suggest that epileptic patients should be tested for antibodies, primarily to GluR3. If positive, long-term immunotherapy should be considered before severe brain surgery. Although neurologists may now be required to accept the tantalizing concept that some human epilepsies have an autoimmune basis and treat their patients accordingly, immunologists and neurobiologists will have to continue to expand their studies of autoimmune epilepsy, as probably only the tip of the iceberg has been discovered so far.