

Neuronal Autoimmune Encephalitis

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Neuronal autoimmune encephalitis comprises a group of autoantibody-mediated inflammatory processes of the CNS attributable to the binding of autoantibodies to neuronal cell antigens. This group includes *limbic encephalitis* (LE) with or without intractable seizures and often with other neurologic symptoms. The correct diagnosis of autoimmune encephalitis depends on awareness and is extremely important because often the encephalitis is completely or partially reversed by immunotherapy with steroids, IV IgG, or plasmapheresis (Davies et al., 2010). This discussion is focused on antibodies to glutamate receptors. However, antibodies related to GABA_B and glycine receptors, GAD, as well as to VGKC and VGCC channel proteins (Malter et al., 2010), neoplasms and paraneoplastic syndromes have also been found causative of encephalitis. See Graus et al. for a detailed review (Graus et al., 2010).

Antibodies associated with encephalitis syndromes usually recognize antigenic neuronal epitopes at pre- or postsynaptic locations, particularly receptors and ion channels. The pathogenicity of these antibodies is proved by (1) demonstrating their binding to specific antigens in brain tissue, (2) response of symptoms to immunotherapy, and (3) correlation between antibody titers in serum or CSF with the neurologic outcome.

The glutamate receptor antigens associated with encephalitis so far discovered include NR1/NR2 subunits of the NMDA receptor, and GluR1/2 and GluR3 subunits of the AMPA receptor. Anti-NMDA GluR[epsilon]2 (same as NR2) has also been found in chronic epilepsy partialis continua (Takahashi et al., 2003). In addition, antibodies against mGluR1 have been found in two cases of cerebellar ataxia and Hodgkin's lymphoma.

Mechanisms of Injury

Antibodies against glutamate receptors may interfere with their protein–protein interactions in the membrane with co-localized gelatinase, which is involved with synaptic and dendritic remodeling. The antibody binding may lead to alterations in dendritic plasticity and synaptic density (Gawlak et al., 2009). Antibodies to AMPA receptor found in LE produce alterations in synaptic receptor location. Application of these antibodies to cultures of neurons decreased the number of GluR2-containing AMPA receptor clusters at synapses and a decrease in AMPAR cluster density. These effects were reversed after antibody removal (Lai et al., 2009). Other possible mechanisms of injury are that antibodies may induce release of microglial factors that enhance NMDA receptor currents and toxicity (Moriguchi et al., 2003), bind to GluR on T cells to trigger inflammatory responses (Ganor et al., 2003), or be induced by elements of cell debris after T-cell–mediated damage (Takahashi et al., 2003) or apoptosis (Muñoz et al., 2010). In addition, GluR antibodies may block their activation or prevent their closing. In Rasmussen’s encephalitis with intractable seizures, for example, serum antibodies to AMPA receptor GluR3 were found to maintain the receptors in a prolonged open state (Twyman et al., 1995), thus leading to intractable seizures and neuronal death (Levite et al., 1999).

Potential Therapy

In rat brain, neuroinflammation can be reduced by antagonism of glutamatergic transmission or inhibition of COX2 activity (Willard et al., 2000). In this view, inhibitors of NMDA receptors, iNOS or COX2 may be potential routes of therapy in these encephalitides.

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