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Diagnostic and Pathogenic Significance of Glutamate Receptor Autoantibodies

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Autoantibodies against glutamate receptors, first reported in Rasmussen encephalitis, have been observed in other focal epilepsies, central nervous system ischemic infarcts, transient ischemic attacks, sporadic olivopontocerebellar atrophy, systemic lupus erythematosus, and paraneoplastic encephalopathies. The detection of glutamate receptor autoantibodies is not useful in the evaluation of Rasmussen encephalitis but may be a biomarker for brain ischemia, and it is helpful in diagnosing certain paraneoplastic encephalopathies. Passive transfer of glutamate receptor autoantibodies from patients with systemic lupus erythematosus or paraneoplastic encephalopathy suggests that glutamate receptor autoantibodies can actively contribute to neurologic dysfunction.

More than 100 autoantibodies that recognize known antigens have been documented in human diseases, and many of these autoantibody-associated diseases involve the nervous system. Some autoantibodies (eg, those against nicotinic acetylcholine receptors in myasthenia gravis) have been established as the proximate cause of neurologic deficits. Others (eg, anti-HuD in paraneoplastic encephalomyelitis), although not known to be pathogenic, are helpful in differential diagnosis.[1]

In 1994, autoantibodies against the ionotropic glutamate receptor protein GluR3 were reported in 3 of 4 children with Rasmussen encephalitis.[2] Plasma exchange resulted in transient improvement in seizure control and cognition in 1 of the 3 autoantibody-positive children. Since that initial article, plasma and cerebrospinal fluid autoantibodies that recognize GluR3 and other glutamate receptor proteins have been described in focal epilepsies, systemic lupus erythematosus (SLE), central nervous system (CNS) ischemia, and paraneoplastic encephalopathies. We discuss the diagnostic utility and pathophysiologic significance of these autoantibodies.

GLUTAMATE RECEPTORS

Glutamate receptors transduce excitatory signals from glutamatergic presynaptic terminals to postsynaptic neurons. Glutamate receptors are also expressed by nonneuronal cells, including neuroglia and T lymphocytes, where, as in neurons, they serve to convey glutamate signals across the plasma membrane. Glutamate receptors are classified into 2 broad groups based on their structures and modes of operation: ionotropic glutamate receptors are heterotetrameric or homotetrameric channels that are opened by glutamate, thus causing sodium influx and plasma membrane depolarization, and metabotropic glutamate receptors are plasma membrane homodimers that modulate enzyme and channel functions and gene transcription via second

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messenger dependent mechanisms. The composition and some properties of these receptors are outlined in Table 1.

DISEASE ASSOCIATIONS OF GLUTAMATE RECEPTOR AUTOANTIBODIES

Table 2 summarizes the neurologic disorders in which GluR autoantibodies have been reported. Since the initial publication by Rogers et al,[2] the case for an association between Rasmussen encephalitis and GluR3 autoantibodies has been weakened by the failure to detect GluR3 antibodies in many patients who meet the clinical and pathologic criteria for diagnosis of this disorder and by the demonstration of GluR3 autoantibodies in patients with noninflammatory focal epilepsies.[3-7] Serum and cerebrospinal fluid NR2B autoantibodies have been reported in patients with Rasmussen encephalitis and were found in other forms of chronic epilepsia partialis continua and in nonherpetic acute limbic encephalitis but not in patients with the Lennox-Gastaut syndrome or infantile spasms (West syndrome). In patients in whom serial autoantibody assays were available, IgM antibodies appeared after the onset of seizures and later became undetectable.[8,9] NR2A/NR2B autoantibodies are detectable in more than a third of patients with SLE.[10,11] Whether titers of these autoantibodies correlate with abnormalities in cognition and other neuropsychiatric complications of SLE remains controversial.[11-16]

Elevated titers of IgG autoantibodies against an NR2A/NR2B peptide have been reported in patients with acute ischemic infarction or transient ischemic attack. These autoantibodies were not present in patients with intracerebral hemorrhage or hypertension without neurologic deficits. There was a strong correlation between antibody titer and severity of neurologic deficits in the ischemic infarction group.[17] The same laboratory has subsequently reported that an elevated preoperative titer of NR2 autoantibodies was highly predictive of poor neurologic outcome after cardiac surgery in high-risk surgical patients.[18] These results suggest that *N*-methyl-D-aspartate receptor autoantibodies are biomarkers for CNS ischemia, but this requires confirmation by other laboratories. Furthermore, the 2-fold increase in IgG autoantibody titers within 12 hours after admission to the intensive stroke unit that these investigators reported in patients with ischemic infarction[17] seems unusually rapid for even a memory B-cell antibody response.

Autoantibodies against the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor (AMPAR) subunit proteins GluR1 and GluR4, the kainate receptor subunit protein GluR5, the *N*-methyl-D-aspartate receptor NR1/NR2 heteromers, and the metabotropic receptor subunit protein mGluR1 have been well characterized in paraneoplastic syndromes.[19-22] Antibodies that bound to NR1/NR2B heteromers but not to individual *N*-methyl-D-aspartate receptor subunit proteins were found in the serum samples and cerebrospinal fluids of 12 women with teratomas and paraneoplastic encephalitis but not in patients with other paraneoplastic and nonparaneoplastic forms of encephalitis.[22]

MECHANISMS THAT MAY INITIATE GLUTAMATE RECEPTOR AUTOANTIBODY PRODUCTION

Whereas CNS-specific antigens are normally shielded from the systemic immune system, infarction and other pathologic processes in which cellular necrosis occurs could result in the release of antigenic glutamate receptor peptides from the CNS for processing by the peripheral immune system. In Rasmussen encephalitis and other inflammatory disorders, release of glutamate receptor antigens to the periphery might not be required. Instead, antigen presentation and autoantibody production could be initiated by immune cells already resident in the CNS. Peripheral tissues may also provide glutamate receptor peptides to antigen-presenting cells. For example, T lymphocytes express GluR3-containing AMPARs, and their GluR3 undergoes proteolytic cleavage during T-lymphocyte activation.[23] In the paraneoplastic

encephalopathy associated with ovarian teratomas, glutamate receptors expressed by neurons in the teratomas may serve as the source of *N*-methyl-D-aspartate receptor heteromers for autoantibody production.[22] Finally, glutamate receptor autoantibody production might be owing to molecular mimicry. This phenomenon has been well documented in mice that develop autoantibodies against multiple AMPAR subunit proteins when infected with murine leukemia virus.[24] A well-documented example in rabbits and mice that may occur in humans with SLE is the production of autoantibodies that recognize double-stranded DNA epitopes and NR2A/NR2B after sensitization to an NR2 peptide.[10,14,25,26]

NEUROBIOLOGIC EFFECTS OF GLUTAMATE RECEPTOR AUTOANTIBODIES

Are glutamate receptor autoantibodies pathogenic? Animal studies suggest that they can be. Rabbits immunized with an NR2B or GluR3 peptide develop seizures, and rabbit GluR3 autoantibodies can activate AMPARs expressed by transfected oocytes and cultured neuronal AMPARs and kill the cultured neurons by means of a complement-dependent mechanism.[2,27-29] Mouse anti-GluR3 peptide antibodies activate AMPARs and induce excitotoxicity in cultured neurons,[30] and mice immunized with either NR2/NR3 or GluR3 peptides demonstrate CNS neuronal loss in vivo.[26,30] One study[31] argues that glutamate receptor antibodies can also be neuroprotective; rats expressing high-titer NR1 autoantibodies were refractory to kainate-induced seizures and were partially protected against forebrain ischemic infarction. This observation requires confirmation by other laboratories.

With respect to the pathogenicity of human glutamate receptor autoantibodies, more than a decade has passed since the initial report of a therapeutic response to plasma exchange in Rasmussen syndrome, but support for the pathogenicity of glutamate receptor autoantibodies in this disorder is still equivocal. Many patients with Rasmussen encephalitis do not have detectable GluR3 autoantibodies, and a consensus has not yet been reached as to whether progressive CNS damage in this disorder is mediated by autoantibodies, pathogenic T lymphocytes, or both.[32]

There is preliminary evidence of the neuropathogenicity of glutamate receptor autoantibodies in SLE, sporadic olivopontocerebellar atrophy, and paraneoplastic encephalopathies. Stereotaxic injection of autoantibodies prepared from the brain specimen of a patient with SLE and severe encephalopathy killed mouse hippocampal neurons.[14] Encephalopathic patients with NR2A/NR2B autoantibodies showed diffusion-weighted imaging abnormalities in the amygdala that were not present in encephalopathic patients who do not express this class of autoantibodies.[13] GluR2 autoantibodies from a patient with sporadic olivopontocerebellar atrophy activated AMPARs in cultured mouse neurons,[33] and GluR5 autoantibodies from a group of patients with paraneoplastic encephalopathy activated kainate receptor–mediated currents,[19] thus suggesting that these autoantibodies are capable of inducing neuronal excitotoxicity. Perhaps the strongest evidence of a pathophysiologic role for glutamate receptor autoantibodies was obtained in 2 patients who, while in remission from Hodgkin disease, developed severe cerebellar ataxia and expressed mGluR1 autoantibodies that blocked glutamate-induced inositol phosphate formation. These autoantibodies, when administered intrathecally to mice, elicited reversible ataxia.[20,21]

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REFERENCES

1. Vincent A, Lang B, Kleopa KA. Autoimmune channelopathies and related neurological disorders. Neuron 2006;52(1):123–138. Medline:17015231. [PubMed: 17015231]
2. Rogers SW, Andrews PI, Gahring LC, et al. Autoantibodies to glutamate receptor GluR3 in Rasmussen's encephalitis. Science 1994;265(5172):648–651. Medline:8036512. [PubMed: 8036512]
3. Wiendl H, Bien CG, Bernaconi P, et al. GluR3 antibodies: prevalence in focal epilepsy, but no specificity for Rasmussen's encephalitis. Neurology 2001;57(8):1511–1514. Medline:11673604. [PubMed: 11673604]
4. Mantegazza R, Bernasconi P, Baggi F, et al. Antibodies against GluR3 peptides are not specific for Rasmussen's encephalitis but are also present in epilepsy patients with severe, early onset disease and intractable seizures. J Neuroimmunol 2002;131(1-2):179–185. Medline:12458050. [PubMed: 12458050]
5. Watson R, Jiang Y, Bermudez I, et al. Absence of antibodies to glutamate receptor type 3 (GluR3) in Rasmussen's encephalitis. Neurology 2004;63(1):43–50. Medline:15249609. [PubMed: 15249609]
6. Ganor Y, Goldberg-Stern H, Lerman-Sagie T, et al. Autoimmune epilepsy: distinct subpopulations of epilepsy patients harbor serum autoantibodies to either glutamate/AMPA receptor GluR3, glutamate/NMDA receptor subunit NR2A or double-stranded DNA. Epilepsy Res 2005;65(1-2):11–22. Medline:15978777. [PubMed: 15978777]
7. Kimura A, Sakurai T, Suzuki Y, et al. Autoantibodies against glutamate receptor ε_2-subunit detected in a subgroup of patients with reversible autoimmune limbic encephalitis. Eur Neurol 2007;58(3):152–158. Medline:17622721. [PubMed: 17622721]
8. Takahashi Y, Mori H, Mishina M, et al. Autoantibodies to NMDA receptor in patients with chronic forms of epilepsia partialis continua. Neurology 2003;61(7):891–896. Medline:14557555. [PubMed: 14557555]
9. Mochizuki Y, Mizutani T, Isozaki E, et al. Acute limbic encephalitis: a new entity? Neurosci Lett 2006;394(1):5–8. Medline:16364542. [PubMed: 16364542]
10. DeGiorgio LA, Knostantinov KN, Lee SC, et al. A subset of lupus anti-DNA antibodies cross-reacts with the NR2 glutamate receptor in systemic lupus erythematosus. Nat Med 2001;7(11):1189–1193. Medline:11689882. [PubMed: 11689882]
11. Husebye ES, Sthoeger ZM, Dayan M, et al. Autoantibodies to a NR2A peptide of the glutamate/NMDA receptor in sera of patients with systemic lupus erythematosus. Ann Rheum Dis 2005;64(8):1210–1213. Medline:15708887. [PubMed: 15708887]
12. Yoshio T, Onda K, Nara H, Minota S. Association of IgG anti-NR2 glutamate receptor antibodies in cerebrospinal fluid with neuropsychiatric systemic lupus erythematosus. Arthritis Rheum 2006;54(2):675–681. Medline:16447246. [PubMed: 16447246]
13. Emmer BJ, van der Grond J, Steup-Beekman GM, Huizinga TW, van Buchem MA. Selective involvement of the amygdala in systemic lupus erythematosus. PLoS Med 2006;3(12):e499. doi: 10.1371/journal.pmed.0030499. Medline:17177602. [PubMed: 17177602]
14. Kowal C, DeGiorgio LA, Lee JY, et al. Human lupus autoantibodies against NMDA receptors mediate cognitive impairment. Proc Natl Acad Sci U S A 2006;103(52):19854–19859. Medline:17170137. [PubMed: 17170137]
15. Lapteva L, Nowak M, Yarboro CH, et al. Anti-*N*-methyl-D-aspartate receptor antibodies, cognitive dysfunction, and depression in systemic lupus erythematosus. Arthritis Rheum 2006;54(8):2505–2514. Medline:16868971. [PubMed: 16868971]
16. Steup-Beekman G, Steens S, van Buchem M, Huizinga T. Anti-NMDA receptor autoantibodies inpatients with systemic lupus erythematosus and their first-degree relatives. Lupus 2007;16(5):329–334. Medline:17576734. [PubMed: 17576734]
17. Dambinova SA, Khounteev GA, Izykenova GA, et al. Blood test detecting autoantibodies to *N*-methyl-D-aspartate neuroreceptors for evaluation of patients with transient ischemic attack and stroke. Clin Chem 2003;49(10):1752–1762. Medline:14500616. [PubMed: 14500616]
18. Bokesch PM, Izykenova GA, Justice JB, et al. NMDA receptor antibodies predict adverse neurological outcome after cardiac surgery in high-risk patients. Stroke 2006;37(6):1432–1436. Medline:16627793. [PubMed: 16627793]

19. Carlson NG, Gahring LC, Rogers SW. Identification of the amino acids on a neuronal glutamate receptor recognized by an autoantibody from a patient with paraneoplastic syndrome. J Neurosci Res 2001;63(6):480–485. Medline:11241583. [PubMed: 11241583]
20. Coesmans M, Smitt PA Sillevis, Linden DJ, et al. Mechanisms underlying cerebellar motor deficits due to mGluR1-autoantibodies. Ann Neurol 2003;53(3):325–336. Medline:12601700. [PubMed: 12601700]
21. Smitt, P Sillevis; Kinoshita, A.; De Leeuw, B., et al. Paraneoplastic cerebellar ataxia due to autoantibodies against a glutamate receptor. N Engl J Med 2000;342(1):21–27. Medline:10620645. [PubMed: 10620645]
22. Dalmau J, Tüzün E, Wu H-Y, et al. Paraneoplastic anti-*N*-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007;61(1):25–36. Medline:17262855. [PubMed: 17262855]
23. Ganor Y, Teichberg VI, Levite M. TCR activation eliminates glutamate receptor GluR3 from the cell surface of normal human T cells, via an autocrine/paracrine granzyme B-mediated proteolytic cleavage. J Immunol 2007;178(2):683–692. Medline:17202328. [PubMed: 17202328]
24. Koustova E, Sei Y, Fossom L, et al. LP-BM5 virus-infected mice produce activating autoantibodies to the AMPA receptor. J Clin Invest 2001;107(6):737–744. Medline:11254673. [PubMed: 11254673]
25. Rai G, Ray S, Shaw RE, et al. Models of systemic lupus erythematosus: development of autoimmunity following peptide immunizations of noninbred pedigreed rabbits. J Immunol 2006;176(1):660–667. Medline:16365462. [PubMed: 16365462]
26. Huerta PT, Kowal C, DeGiorgio LA, et al. Immunity and behavior: antibodies alter emotion. Proc Natl Acad Sci U S A 2006;103(3):678–683. Medline:16407105. [PubMed: 16407105]
27. Cohen-Kashi Malina K, Ganor Y, Levite M, Teichberg VI. Autoantibodies against an extracellular peptide of the GluR3 subtype of AMPA receptors activate both homomeric and heteromeric AMPA receptor channels. Neurochem Res 2006;31(10):1181–1190. Medline:16967334. [PubMed: 16967334]
28. He X-P, Patel M, Whitney KD, et al. Glutamate receptor GluR3 antibodies and death of cortical cells. Neuron 1998;20(1):153–163. Medline:9459451. [PubMed: 9459451]
29. Levite M, Fleidervish IA, Schwarz A, et al. Autoantibodies to the glutamate receptor kill neurons via activation of the receptor ion channel. J Autoimmun 1999;13(1):61–72. Medline:10441169. [PubMed: 10441169]
30. Ganor Y, Gottlieb M, Eilam R, et al. Immunization with the glutamate receptor-derived peptide GluR3B induces neuronal death and reactive gliosis, but confers partial protection from pentylenetetrazole-induced seizures. Exp Neurol 2005;195(1):92–102. Medline:15907325. [PubMed: 15907325]
31. During MJ, Symes CW, Lawlor PA, et al. An oral vaccine against NMDAR1 with efficacy in experimental stroke and epilepsy. Science 2000;287(5457):1453–1460. Medline:10688787. [PubMed: 10688787]
32. Bien CG, Granata T, Antozzi C, et al. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: a European consensus statement. Brain 2005;128(pt 3):454–471. Medline:15689357. [PubMed: 15689357]
33. Gahring LC, Rogers SW, Twyman RE. Autoantibodies to glutamate receptor subunit GluR2 in nonfamilial olivopontocerebellar degeneration. Neurology 1997;48(2):494–500. Medline:9040745. [PubMed: 9040745]

Table 1

Glutamate Receptor Protein Subunit Composition and Properties

Glutamate Receptor	Protein Subunits	Receptor Properties
Ionotropic receptors		
NMDAR	NR1, NR2A,[a] NR2B,[a] NR2C, NR2D, NR3A, and NR3B	Heterotetrameric; calcium permeability high; long channel open time
AMPAR	GluR1,[a] GluR2, edited GluR2, GluR3,[a] and GluR4[a]	Heterotetrameric; calcium permeability low if edited GluR2, otherwise moderate; short channel open time
Kainate receptor	GluR5,[a] GluR6, GluR7, KA1, and KA2	Homotetrameric or heterotetrameric; calcium permeability low; short channel open time
Metabotropic receptors		
Group 1	mGluR1[a] and mGluR5	Homodimeric; signals via phospholipase C
Group 2	mGluR2 and mGluR3	Homodimeric; signals via adenylyl cyclase
Group 3	mGluR4, mGluR6, mGluR7, and mGluR8	Homodimeric; signals via adenylyl cyclase

Abbreviations: AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor; NMDAR, *N*-methyl-D-aspartate receptor.

[a]Glutamate receptor protein subunits for which human autoantibodies have been reported.

Table 2

Glutamate Receptor Autoantibodies Reported in Human Neurologic Disorders

Neurologic Disorder	Glutamate Receptor Autoantibody Specificities
Rasmussen encephalitis	GluR3 and NR2B
Other focal epilepsies	GluR3, GluR1, and NR2B
Nonherpetic acute limbic encephalitis	NR2B
Paraneoplastic encephalopathies	NR2A, NR2B, GluR5, and mGluR1
Olivopontocerebellar atrophy, sporadic	GluR2
Ischemic infarction and TIA	NR2A and NR2B
Systemic lupus erythematosus	NR2A and NR2B

Abbreviation: TIA, transient ischemic attack.