# Destroying the Brain through Immunity

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The brain has long been viewed as somewhat protected from attack by the body's immune system. Apart from the autoimmune disease multiple sclerosis, in most of the brain disorders that have been studied, such as epilepsy, stroke, Alzheimer's disease and Parkinson's disease, the immune system was not believed to play a major role. However, in recent years there has been a revolution in neuroimmunology, and a new class of nervous system disorders has been discovered. Termed "synaptic encephalitidies," these disorders are defined by antibodies that target specific proteins located at synapses, the sites where neurons transmit signals to each other. At this time, antibodies to just over half a dozen distinct synaptic targets have been identified; each type of antibody is found in a distinct disease. The common theme, however, is that the antibodies change the function of synapses, altering neuronal communication and leading to dramatic brain dysfunction. These diseases challenge the traditional view of the central nervous system as immune protected.

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Exclusive of the brain, it long has been recognized that nerves and muscles can be a target of antibodies, most famously in the disorder known as myasthenia gravis. Acetylcholine receptors, responsible for transmitting signals from motor neurons to muscle fibers, are targeted by antibodies in this disease, leading to their destruction. This results in debilitating weakness, but it can be treated with immunosuppression. In synaptic encephalitidies, the targets are analogous proteins in brain synapses, including glutamate receptors, GABA receptors, and ion channel modulators. Similar to myasthenia gravis, the antibodies in these disorders are thought to be damaging, and treatments that lower antibody levels produce clinical improvement. Most commonly, these occur in association with tumors (termed paraneoplastic processes as these reflect the remote effects of neoplasms), probably because the tumors mimic nervous system tissues and incite an immune response that spreads to the brain. However, in many cases, these disorders can also appear after viral infections, or for as yet unknown reasons.

In the past, antibodies to neuronal proteins had been identified in association with a variety of neurologic syndromes. However, these antibodies, which usually recognize proteins hidden deep inside of neurons, were thought to reflect an immune response to sick or dying neurons – that is, they were signs of an ongoing process of neuronal injury, rather than its cause. The novel feature of these newly described synaptic encephalitidies is that the antibodies themselves seem to be able to cause the disease, and do not simply represent a marker of disease.

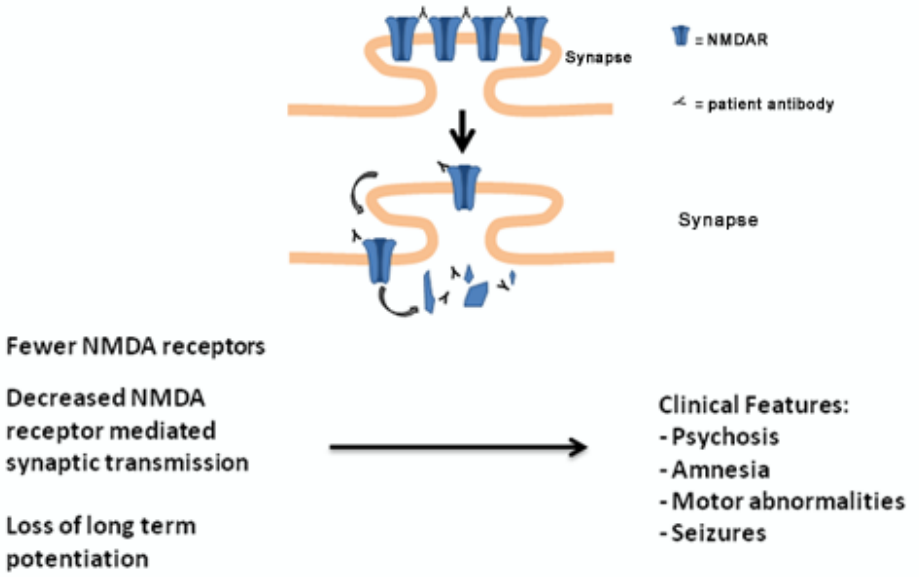
In the most well characterized synaptic encephalitidies, the antibodies are directed to glutamate receptors, particularly the N-methyl-D aspartate receptor (NMDA receptor), a crucial neurotransmitter receptor for learning and memory. Patients can start with days to weeks of personality changes, confusion, hallucinations, paranoia, and memory loss, before eventually developing seizures, abnormal involuntary movements, erratic blood pressure and heart rate swings, and reduced breathing. In its most severe form, the disease is fatal if not treated by reducing antibody levels. However, with treatment most patients recover, back to their normal state of health.

When applied to neurons, patients' antibodies have been shown to cause NMDARs to be lost from synapses. The antibodies appear to be directed to a small region on the NR1 subunit of the NMDA receptor, which represents the ion channel component

of the receptor. This region is accessible in living neurons, showing that it can be a direct target of the antibodies, which then bind and cause receptor loss (Figure 1). Neurons treated with these antibodies have reduced electrical currents transmitted through NMDA receptors; treated neurons are unable to perform a type of synaptic learning called long term potentiation (LTP), perhaps explaining the amnesia frequently experienced by patients. Interestingly, reduced NMDA receptor function has been proposed as a cause of schizophrenia. The loss of NMDA receptors in this encephalitis can thus create a schizophrenia-like state, resulting in hallucinations, paranoia, and psychosis.

pruning" identified in basic science studies (termed LTD, or long term depression), providing a direct link between cellular investigations and what happens in the human disease. The clinical symptoms match what would be predicted from the laboratory studies. As other synaptic encephalitidies become more fully understood, they may reveal paradigms through which other neurotransmitter receptors influence human behavior.

Initially thought to be rare, anti-NMDAR encephalitis is now the most commonly identified form of encephalitis. With time the other synaptic encephalitidies are also likely to rise in prevalence.




Similarly, syndromes have been characterized in association with other glutamate receptors, such as AMPA, mGuR5 and mGLuR1. Individuals with disease-causing antibodies to the AMPA type of glutamate receptors, present most frequently with memory loss and seizures, without prominent hallucinations. Individuals with antibodies to mGluR5 have been identified as having "Ophelia syndrome," in which patients with Hodgkin's lymphoma develop encephalitis and dementia. In contrast, subjects with antibodies to mGLuR1 develop a different syndrome, with severe balance problems (cerebellar ataxia). Such findings illustrate the selectivity of clinical syndromes for specific antibodies.

These findings also reveal the importance of individual neurotransmitter receptors in ongoing brain function and dysfunction. For example, in anti-AMPAR encephalitis, the disease is thought to be caused by internalization of AMPARs at synapses. This internalization mirrors a type of cellular "memory

Although each disorder has a "typical presentation," with increasing experience, a wide variety of symptoms has been seen, as well as patients with either isolated symptoms (such as seizures only) or very mild symptoms. This expansion of the disease spectrum has led to the possibility that synaptic encephalitidies, particularly anti-NMDAR encephalitis, may sometimes mimic more common disorders, leading to missed diagnoses of this treatable disease.

Evidence of this possibility is decidedly mixed. Individuals with rapidly progressive neurological diseases, such as those believed to have Creutzfeldt Jakob disease (CJD), occasionally harbor antibodies to synaptic components, although individuals with biopsy proven CJD never do. This suggests that some people are misdiagnosed with CJD, but actually have synaptic encephalitidies. Even more controversial is the possibility that patients with schizophrenia or autism may have anti-NMDAR encephalitis. Very

few patients with typical forms of these disorders have been found to have anti-NMDAR encephalitis, but rare individuals with such misdiagnoses may conceivably exist.

Perhaps the most important aspect of synaptic encephalitidies is that they are amenable to treatment. This treatment may take several forms beyond symptomatic treatment of neurological symptoms. First, if there is a tumor triggering the immune response, it should be treated or removed. In addition, the antibodies themselves can be targeted for removal by plasmapheresis or intravenous gamma globulin. Finally, bold immunomodulatory therapies targeting specific immune cells may be needed in some situations. Together these change synaptic encephalitidies from deadly disorders to diseases that can often be cured or at least controlled, leading to minimal long-term disability in many patients.

There are many things still to learn about these newly discovered disorders. At the most basic level, no purified antibody has ever been shown to cause the disruption to receptor function or transmit the disease. This is because these antibodies are highly conformationally specific and are therefore not readily purified, as the needed techniques alter receptor shape too much. Thus, patient derived spinal fluid or total antibodies from patients' blood is the smallest pure unit proven to mediate the disorders. *In vitro* purification or production of disease causing antibodies is needed. Purified antibodies could be used to definitively show that they are able to directly cause these diseases, and would allow researchers to search for ways to disrupt their interactions with synaptic proteins.

In addition, these antibodies could be used as tools for understanding the function of the nervous system. For example, in laboratory studies, antibodies could be applied to specific brain regions, providing long term receptor modulation, and allowing neuroscientists to determine the behavioral consequences of this change in receptor function. Finally, the underlying mechanisms of synaptic encephalitidies remain incompletely understood. While all appear to lead to loss of functional receptors, how they do this is unclear. Do they create novel pathways for removal of receptors from neuronal surfaces, or utilize the homeostatic mechanisms that are already in place? Understanding these and other questions will place synaptic encephalitidies in the realm of disorders that, in the study of their underlying disease mechanisms, also inform us about the basic functions of the human brain.

## Further Reading

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