**Glycine receptor antibodies in PERM: a new channelopathy**

This scientific commentary refers to ‘Glycine receptor antibodies in PERM and related syndromes: characteristics, clinical features and outcomes’, by Carvajal-González et al. (doi:10.1093/brain/awu142).

Ligand- or voltage-gated ion channels can be affected by mutation or autoimmune attack, leading to so-called channelopathies. A number of CNS disorders, such as limbic encephalitis and certain forms of epilepsy, have been shown to associate with specific serum autoantibodies against ion channels or related proteins (Irani and Lang, 2008). In 2008, the glycine receptor (GlyR) was first recognized as a possible target for autoantibodies in a patient with progressive encephalomyelitis, rigidity and myoclonus (PERM) (Hutchinson et al., 2008). The GlyR is a member of a superfamily of ligand-gated ion channels that also includes N-methyl-D-aspartic acid (NMDA) receptors and nicotinic acetylcholine receptors. GlyRs are present throughout the brain, but are most abundant in the spinal cord and brainstem. The GlyR is also the target of the alkaloid strychnine, which causes generalized muscle spasms and cramps, muscle stiffness and tightness, agitation, heightened awareness and responsiveness, stimulation-evoked seizures, myoclonus, respiratory failure, and sometimes death. For comparison, the symptoms of PERM include muscle spasms, cramps, myoclonus, stimulus-evoked startle and respiratory failure. In this issue of *Brain*, Carvajal-González et al. (2014) report the presence of antibodies against the GlyR in a relatively large cohort of patients with PERM, and describe the characteristics and clinical features of these patients. Using cellular assays, the authors present strong evidence that GlyR antibodies are the causative agents in this disorder.

The main clinical significance of this paper is that it demonstrates that PERM is a treatable autoimmune disease. There is considerable symptom overlap between PERM, stiff person syndrome and neumyotonia. Moreover, antibodies against glutamic acid decarboxylase and the voltage-gated potassium channel complex have been detected in both PERM and stiff person syndrome. In the current study, Carvajal-González et al. prospectively identified 52 patients with GlyR antibodies, and classified 33 of these as PERM, two as stiff person syndrome and five as limbic encephalitis or epileptic encephalopathy. Patients with PERM were initially identified by the presence of GlyR antibodies, but the final classification was based on Meinck and Thomson (2002) and Espay and Chen (2006), in which PERM is defined on the basis of brainstem involvement in addition to the axial or limb rigidity typical of stiff person syndrome. Notably, autonomic disturbances were marked in many patients, and respiratory failures may have contributed to two of the four hospital deaths during the study. Another clinically important observation was the association of thymomas and lymphomas with PERM, as stiff person syndrome is more often associated with breast and lung cancer. The role of amphiphysin and gephyrin autoantibodies, previously detected in stiff person syndrome, remains to be characterized in PERM.

How do pathogenic immunoglobulins such as anti-GlyR antibodies gain access to the brain? Antibodies typically have only a limited ability to cross the blood–brain barrier. However, there is a large body of evidence indicating that pathogenic autoantibodies can enter the CNS (for a review see Martinez-Martinez et al., 2013). The mechanisms by which antibodies manage to cross the blood–brain barrier under normal conditions are still unclear, but the blood–brain barrier is known to become 10-times more permeable following local inflammatory reactions (Cutler et al., 1970). Some CNS autoimmune channelopathies occur only when the integrity of the blood–brain barrier is disrupted and an increased number of antibodies and/or lymphocytes gain access to the brain (Martinez-Martinez et al., 2013). On the basis of the ratio of GlyR antibodies to total immunoglobulins in serum and CSF, Carvajal-González et al. concluded that there was intrathecal synthesis of GlyR antibodies in three of six patients for whom matching serum and CSF samples were available. However, this was not true of all patients, thus we must assume that there was substantial antibody access to the brain.

Most patients in the study benefited substantially from immunotherapy. This suggests that the autoantibodies cause only limited neuronal cell death and instead affect GlyR functions.
directly. Carvajal-González and colleagues used in vitro studies to analyse GlyR autoantibody effector mechanisms. Their results clearly indicate that GlyR antibodies degrade their target by antigenic modulation. Moreover, because a large proportion of the GlyR antibodies were of the IgG1 and IgG3 isotypes, they also activated complement on GlyR-expressing cells in vitro. To what extent these mechanisms contribute to pathology in vivo is likely to depend on how densely GlyRs are clustered by their anchoring protein gephyrin. At the neuromuscular junction, expression of such anchoring proteins was shown to strongly affect antigenic modulation of ion channels by autoantibodies in vivo (Martinez-Martinez et al., 2007, for review see Souroujon et al., 2010). It would be useful to establish an active immunization with GlyR, or a passive transfer animal model with patient-derived monoclonal GlyR antibodies, to investigate pathogenic mechanisms and to test symptomatic or immunosuppressive therapies, or complement inhibitors. Given that some patients did not respond to sustained immunosuppressive treatment, there might be a role for plasma cell targeting therapies (Gomez et al., 2012) in the treatment of PERM to rapidly reduce autoantibody production. In this regard, studies in another antibody-mediated neurological disease, myasthenia gravis, could provide a valuable reference (Souroujon et al., 2010). Additionally, it would be interesting to use electrophysiological methods to address the question of whether GlyR antibodies have any direct effects on their target. Such effects could include competitive or allosteric impairment of ligand binding, or alternatively, impairment of ion channel function independent of ligand binding. In either case, this would cause a diminished chloride ion influx, and thus reduced neuronal inhibition, upon release of glycine from nerve terminals. This would lead to PERM being defined as a GlyR channelopathy, being the autoimmune counterpart of hereditary hyperekplexia caused by GlyR mutations (OMIM 138491). It should be noted that there are other chloride channelopathies—namely the Thomsen and Becker types of myotonia congenita—which are caused by mutation of the CLCN1 gene that codes for the voltage-dependent CLC-1 chloride channel in skeletal muscle. These mutations reduce chloride channel function, leading to hyperexcitability, delayed relaxation and stiffness of muscle fibres.

What is the physiological effect of reduced chloride currents in excitable tissue? The Nernst equilibrium potential for chloride ions is about −70 mV, which is identical or very close to the resting potential of neurons. Thus, when chloride channels open, the membrane potential does not change very much, but any depolarizing input will be strongly dampened because the electrical charge carried by sodium ions entering the neuron will be shunted by the chloride ion conductance. Overall, impaired function of mutated voltage-dependent chloride channels in muscle, or impairment of ligand-gated chloride channels in the brainstem and spinal cord, causes hyperexcitability, leading either to myotonia or the encephalomyelitis and rigidity seen in PERM.

The message for clinicians is that many brain disorders, or subgroups of them, may be caused by autoantibodies. This extends also to psychiatry, where a number of syndromes seem to have subgroups in which autoantibodies are involved. Moreover, the possibility of a paraneoplastic origin should be investigated in autoantibody-positive patients. The fact that antibody ‘attack’ in the brain does not necessarily involve neuronal damage gives reason to be hopeful as symptoms can be expected to disappear following immunotherapy. However, as long as the production of antibodies persists, sustained immunosuppression may be required.

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