

## Stiff person syndrome-associated autoantibodies to amphiphysin mediate reduced GABAergic inhibition

Christian Geis  
Andreas Weishaupt  
Stefan Hallermann  
Benedikt Grünewald  
Carsten Wessig  
Thomas Wultsch  
Andreas Reif  
Nadiya Byts  
Marcus Beck  
Sibylle Jablonka

Michael K. Boettger  
Nurcan Üçeyler  
Wernher Fouquet  
Manfred Gerlach  
Hans-Michael Meinck  
Anna-Leena Sirén  
Stephan J. Sigrist  
Klaus V. Toyka  
Manfred Heckmann  
Claudia Sommer

### Summary

Synaptic inhibition is a central factor in the fine tuning of neuronal activity in the central nervous system. Symptoms consistent with reduced inhibition such as stiffness, spasms and anxiety occur in paraneoplastic stiff person syndrome with autoantibodies against the intracellular synaptic protein amphiphysin. Here we show that intrathecal application of purified anti-amphiphysin immunoglobulin G antibodies induces stiff person syndrome-like symptoms in rats, including stiffness and muscle spasms. Using in vivo recordings of Hoffmann reflexes and dorsal root potentials, we identified reduced presynaptic GABAergic inhibition as an underlying mechanism. Anti-amphiphysin immunoglobulin G was internalized into neurons by an epitope-specific mechanism and colocalized in vivo with presynaptic vesicular proteins, as shown by stimulation emission depletion microscopy. Neurons from amphiphysin deficient mice that did not internalize the immunoglobulin provided additional evidence of the specificity in antibody uptake. GABAergic synapses appeared more vulnerable than glutamatergic synapses to defective endocytosis induced by anti-amphiphysin immunoglobulin G, as shown by increased clustering of the endocytic protein AP180 and by defective loading of FM 1–43, a styryl dye used to label cell membranes. Incubation of cultured neurons with anti-amphiphysin immunoglobulin G reduced basal and stimulated release of  $\gamma$ -aminobutyric acid substantially more than that of glutamate. By whole-cell patch-clamp analysis of GABAergic inhibitory transmission in hippocampus granule cells we showed a faster, activity-dependent decrease of the amplitude of evoked inhibitory postsynaptic currents in brain slices treated with antibodies against amphiphysin. We suggest that these findings may explain the pathophysiology of the core signs of stiff person syndrome at the molecular level and show that autoantibodies can alter the function of inhibitory synapses in vivo upon binding to an intraneuronal key protein by disturbing vesicular endocytosis.

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