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INTRINSIC ACTIVITY

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*MEETING ABSTRACT*

## A1.9

### Neuronal pathomechanisms of anti-AMPA receptor autoimmune encephalitis

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**Background:** Anti-AMPA receptor encephalitis patients mostly suffer from limbic encephalitis, including memory loss, psychiatric symptoms and, in approximately a third of the cases, epilepsy. The pathomechanisms leading to these symptoms are incompletely to poorly understood. A body of evidence exists demonstrating that the antibodies lead to internalization of the AMPA receptor as a primary effect, thereby leading to reduced AMPA receptor-mediated excitatory receptor currents. While such reduction of AMPA receptor-mediated neurotransmission can be readily reconciled with memory deficits, the pathogenesis underlying epilepsy in these patients is difficult to understand, considering the compromised neuronal excitation. From previous work on cultured neuronal networks derived from rat, compensatory reductions of inhibitory GABAergic signalling together with enhanced intrinsic (*i.e.* independent of synaptic activity) excitability of the neurons were proposed as possible underlying pathomechanisms. In this study we set out to investigate this possibility by exploring the *in vitro* effects of an anti-AMPA receptor sample (which was derived from a patient who had been tested at the Division of Neuropathology and Neurochemistry) on rat hippocampal neurons.

**Methods:** Patch-clamp electrophysiology was performed on primary rat hippocampal neurons (co-cultured with glial cells) that had been pretreated with the autoimmune sample or control samples for 72 hours. Current-clamp recordings were conducted to measure neuronal membrane voltage and spontaneous or evoked electrical activities, and voltage-clamp experiments served to investigate ionotropic receptor currents either induced by exogenous application of ligands (*e.g.* AMPA or muscimol, a $GABA_A$ receptor agonist) or as spontaneously occurring synaptic events.

**Results:** Our electrophysiological recordings confirm a reduction of neuronal responses to AMPA and of AMPA-elicited receptor currents, as well as of spontaneously occurring excitatory postsynaptic events in anti-AMPA receptor antibody-treated neurons compared to control neurons. Conversely, muscimol-elicited currents remained unaltered, and a reduction of spontaneously occurring inhibitory postsynaptic events was also not observed. However, the intrinsic neuronal excitability, which was probed by depolarizing current injections of increasing amplitude from a resting voltage set to −80 mV by experimental hyperpolarization, was considerably augmented in anti-AMPA receptor antibody-treated neurons. This effect showed up prominently as an elicitation of high discharge frequencies of action potentials at relatively moderate levels of depolarizing currents (30 to 120 pA). Unprovoked discharge activity was readily observed in neurons treated with control samples, but neurons treated with the anti-AMPA receptor autoimmune sample lacked spontaneous activity in most cases, though discharge activity could always be elicited by current injection. However, it was repeatedly observed that neurons suddenly switched to seizure-like discharge activity during the recordings. Such events were not seen in the control neurons.

**Discussion:** A previous report has proposed homeostatic reduction of $GABA_A$ receptor-mediated inhibitory neurotransmission as a potential cause of epilepsy in anti-AMPA receptor encephalitis patients. While seizure-like activity was also found to arise spontaneously in this study of primary neuronal cultures treated with our anti-AMPA receptor autoimmune sample, a decrease of $GABA_A$ receptor-mediated signalling could not be confirmed as a seizure activity-precipitating mechanism. Instead, potentiation of the intrinsic excitability at relatively moderate depolarization levels appeared to render neurons prone to discharge in abnormally elevated discharge patterns.

**Keywords:** AMPA receptor – autoimmune encephalitis – epilepsy – electrophysiology – hippocampus

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