Excitotoxicity and inflammation in ALS

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Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease due to motor neuron loss and leads to death of the patient within 3 to 5 years after onset of the disease. In approximately 10% of patients, the disorder is inherited in an autosomal dominant manner and missense mutations were found in the superoxide dismutase 1 (SOD1) gene. The pathogenesis of the disease is not yet fully understood. Aberrant enzymatic activity of SOD1, leading to oxidative stress, excitotoxicity and the formation of aggregates of misfolded SOD1, are currently the most important hypotheses. However, the extent to which excitotoxicity contributes to motor neuron death in ALS remains unclear. We therefore tested the effect of the selective AMPA/kainate receptor antagonist NBQX on the survival of mutant (G93A) SOD1 mice, a rodent model of familial ALS. Treatment of G93A mice with NBQX prolonged their survival by 13 days, corresponding to a 10% increase of the life span, confirming that AMPA receptor-mediated excitotoxicity contributes to the motor neuron loss in this model. Recently, in analogy of the findings in other neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease, the role of inflammatory changes found in ALS was investigated. Pathological studies showed that the loss of motor neurons is accompanied by a marked gliosis and proliferation of microglial cell in spinal cords of both patients and transgenic mice. As minocycline has been shown to inhibit microglial activation, the therapeutic efficacy of this tetracycline derivative was tested in the G93A mice. Minocyline dose-dependently delayed disease onset and extended the survival of the G93A mice by 16%. Minocycline clearly protected mice from loss of motor neurons and from vacuolization. These data, in combination with the results obtained with cox-2 inhibitors, indicate that interference with inflammation is also a promising therapeutic strategy for ALS.

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