Selective deletion of AMPA receptors on oligodendrocytes prevents demyelination and axonal injury in autoimmune demyelination

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Background

Although current treatments for multiple sclerosis (MS) reduce disease symptoms and relapses by modulating the immune system, CNS inflammation and disease progression persist. This emphasizes the need for neuroprotective therapies in MS. One promising pathological mechanism to target is excitotoxicity, as neurons and oligodendrocytes (OLs) are vulnerable to damage via excess glutamate, and MS patients have elevated levels of glutamate in the brain as measured by MRI. We previously demonstrated that glutamate release from the system xc- transporter is an important mechanism in demyelination during experimental autoimmune encephalomyelitis (EAE) in mice. However, how glutamate specifically affects OLs during EAE, and whether protecting myelin prevents neurodegeneration, is unclear.

Objectives

The aim of this study is to determine whether deletion of the target for excitotoxic glutamate selectively in OLs, the AMPA receptor (AMPAR), prevents myelin and axonal damage in EAE.

Methods

The GluA4 AMPAR subunit was selectively deleted from OLs in mice as a result of Cre expression under one of two OL-specific promoters: Olig2 or Plp1. Deletion was confirmed with immunohistochemistry, and functional reduction of AMPARs was determined using Cai2+ imaging of ex vivo optic nerves. Mice were subjected to

MOG35-55-induced EAE. To rule out potential effects on the immune system as a result of GluA4 deletion in OLs, CD4+ T cell numbers and phenotypes in spinal cords, and proliferation in spleens, were analyzed with FACS analysis at peak of disease. Extent of demyelination, axonal damage, and reactive gliosis was determined by immunohistochemistry 30 days post-EAE induction using 3D confocal imaging.

Results

Deletion of GluA4 in OLs resulted in reduced Cai2+ after treatment with glutamate, indicating a functional reduction in AMPAR activity. Mice subjected to EAE and deficient in GluA4 selectively on OLs had improved clinical scores and reduced myelin damage in spinal cords. Furthermore, axonal damage in conditional knockout mice was abrogated. No alterations in numbers or phenotypes of CNS-infiltrating CD4+ T cells or proliferation in spleens was observed.

Conclusion

These data support that conditional deletion of the target for excitotoxic glutamate on myelin confers CNS protection that is independent of modulating the immune system. This suggests the importance of maintaining myelin integrity to promote axonal health and prevent neurodegeneration in MS.