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EAAT3 modulation of the oligodendrocyte lineage in *in vitro* and *in vivo* models of Multiple Sclerosis.

L. van Veggel[1,2,5], M. Schepers[1,2,5], A. Tiane[1,2,5], B. Rombaut[1,2,5], J. Royakkers[3], H. Diliën[3], N. Hellings[1,5], P. Moya[4], R. Schreiber[2], T. Vanmierlo[1,2,5]

[1] *BIOMED Biomedical Research Institute, Faculty of Medicine and Life Sciences, Hasselt University, Hasselt, Belgium*
[2] *Department Psychiatry and Neuropsychology, Division of Translational Neuroscience, European Graduate School of Neuroscience, School for Mental Health and Neuroscience, Maastricht University, Maastricht, Netherlands*
[3] *Department of Sensor Engineering, Faculty of Science and Engineering, Maastricht University, Maastricht, Netherlands*
[4] *Facultad de Ciencias, Instituto de Fisiología, Centro Interdisciplinario de Neurociencia de Valparaíso (CINV), Universidad de Valparaíso, Valparaíso, Chile*
[5] *University MS Center (UMSC), Hasselt, Belgium*

Multiple sclerosis is the most common neurodegenerative disorder among adolescents, with 2.5 million people suffering worldwide. When the disease progresses, demyelination due to oligodendrocyte damage leads to neurodegeneration. The eventual inability to recover from this damage is in part due to the vulnerability of oligodendrocyte precursor cells (OPCs) to oxidative stress. No treatment is yet available to target the progression of disease. In this project we aim to protect OPCs from oxidative stress to sustain endogenous remyelination processes. We hypothesise that activation of the excitatory amino acid transporter 3 (EAAT3) in OPCs holds the key to protection from inflammation-induced oxidative stress. EAAT3 is a cysteine transporter, providing the cell with the rate limiting building block for glutathione (GSH) synthesis, the key antioxidant compromised in OPCs. We aim to confirm and elucidate the role of EAAT3 in OPC differentiation and myelination *in vitro*. The effect of EAAT3 modulation was investigated in the context of OPC differentiation (*in vitro*) and remyelination in the EAE model (*in vivo*). Immunohistochemistry was performed to determine the effects of EAAT3 inhibition and lentiviral overexpression on differentiation (MBP and O4). During the chronic EAE, visual evoked potentials (VEPs, both amplitude and latency) were measured to determine effects on de- and remyelination on comparison with vehicle and a positive control, riluzole. Cysteine presence and uptake is crucial for the viability and normal functioning of primary OPCs *in vitro*. Inhibition of EAAT3 decreased the capacity of OPCs to undergo differentiation. These findings provide a rationale to investigate whether activation/overexpression of EAAT3 might prove beneficial for OPC differentiation and thus remyelination.