Altered expression of the GPR17 receptor in the spinal cord of SOD1G93A mice, a model of amyotrophic lateral sclerosis

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Amiotrophic Lateral Sclerosis (ALS) is a devastating neurodegenerative disease due to loss of motor neurons (MN). Recently, oligodendroglia have been implicated in the pathogenesis of ALS. Oligodendrocytes are severely affected during disease and their degeneration has been shown to precede MN death in the mutant SOD1 mouse model. As a consequence, oligodendrocyte precursor cells (OPCs) rapidly react with increased proliferation, but fail to replace degenerating oligodendrocytes. The differentiation capacity of OPCs is also impaired, resulting in the presence of immature and dysfunctional oligodendrocytes, unable to provide MN with trophic and metabolic support (Lee Y et al. 2012 Nature; Kang SH et al. 2013 Nat Neurosci). Restoring oligodendrocyte function and promoting OPC maturation thus emerge as interesting approaches for retard MN degeneration. An important regulator of OPC differentiation and myelination is the membrane P2Y-like receptor GPR17, that is specifically expressed in OPCs in transition to pre-oligodendrocytes, but not in mature cells. We have shown that prevention of the physiological GPR17 downregulation at late OPC stages through forced receptor over-expression results in delayed cell maturation (Fumagalli M et al. 2015 Glia). Accordingly, GPR17 over-expression has been described in several mouse model of CNS degeneration characterized by remyelination failure (Fumagalli M et al. 2016 Neuropharmacol). The involvement of GPR17 has never been studied in the context of ALS pathology.

Here, we used western-blot to analyse GPR17 espression in parallel to the mature oligodendrocyte marker MBP in the SOD1G93A mouse ALS model. Spinal cord lumbar tracts of SOD1G93A mice at different disease stages, ie, before disease onset (Post-Natal Day, PND 30), at disease onset (PND 90) and at later disease stages (PND 120) were compared with age-matched controls. We also examined the metabolic support function of oligodendrocytes by analyzing MCT1, a lactate transporter expressed by these cells. Data showed that the expression of MBP and MCT1 are reduced in lumbar spinal cord of late stage SOD1G93A mice. Reduced levels of MCT1 were also detected in presymptomatic PND30 mice. Of note, GPR17 expression was found to be up-regalated both at early and late disease stages.

The demonstration that GPR17 is altered in ALS suggests that its dysregulation may be involved in the blockade of OPC differentiation contributing to disease development, and that it could represent an adequate new target for therapeutic intervention in ALS.

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