Knocking Down mGluR1 Prolongs Survival And Ameliorates Motor Skills in the SOD1^{G93A} Mouse Model Of ALS

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Amyotrophic lateral sclerosis (ALS) is a progressive and rapidly fatal neurodegenerative disease that involves both upper and lower motor neuron (MN) degeneration, leading to muscles weakness, paralysis and death, due to respiratory failure. At present, the mechanisms underlying the loss of MNs are largely unknown and no effective therapeutic approaches are available, except Riluzole that, however, cannot stop the progression of the disease (Cheung et al.,2006). Glutamate(Glu)-mediated excitotoxicity has been proposed as one of the main cause for neurodegeneration in ALS (Rothstein et al, 1995). On the basis of our previous studies, we suggested that the high plasma and liquor levels of Glu, found in patients and in animal models of the disease, are due not only to the proposed reduced astrocytary Glu transport, that in turn increases Glu availability, but also to abnormal release of the amino acid neurotransmitter (Milanese et al., 2011, 2015).

We recently demonstrated that activation of the Group I metabotropic glutamate receptors (mGluR1 and mGluR5) sited at glutamatergic nerve terminal is responsible for abnormal release of Glu in the spinal cord of SOD1^{G93A} mice, a widely used animal model of the familial forms of ALS (Giribaldi et al., 2013). Prompted by these results, in the present work we generated mice expressing reduced levels of mGluR1 in the SOD1^{G93A} background (SOD1^{G93A}-mGluR1$^{-/+}$), by crossing the SOD1^{G93A} mutant mouse with Grm1$^{+/crv4}$ mouse, lacking of mGluR1 because of a spontaneous recessive mutation. Double mutants mice were analyzed for survival and motor abilities, as well as for biochemical and histological issues linked to ALS.

SOD1^{G93A}-mGluR1$^{-/+}$ showed increased survival, slower disease progression and improved motor skills. Histological examination revealed a higher number of preserved motor neurons in the ventral horns of spinal cord and reduced mitochondrial damage. Biochemical studies showed decreased astrocytes and microglia activation and reduction of the expression of markers characterizing neuronal cell suffering and death.

This study proves that the partial lack of mGluR1 has a significant positive impact on pathology progression in SOD1^{G93A} mice, thus supporting the detrimental role of mGluR1, and may provide the rationale for a pharmacological approach targeting the Group I mGluRs.

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