Reduced Expression of mGlu5 Receptor Improves Survival and Clinical Symptoms in the SOD1^{G93A} Mouse Model of Amyotrophic Lateral Sclerosis

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Amyotrophic lateral sclerosis (ALS) is an adult-onset disease characterized by degeneration of motoneurons (MNs) resulting in muscle weakness, paralysis and death for respiratory failure. The etiology of ALS remains unknown and the mechanism of mSOD1-induced MN damage and death has been ascribed to several neuronal alterations. Glutamate (Glu)-mediated excitotoxicity is still one major factor accountable for neurodegeneration (Vucic *et al.,* 2014). Moreover several *in-vitro* and *in-vivo* studies demonstrate that damage within MNs is also sustained by pathologic degeneration occurring in non-neuronal neighboring cells (Boillée *et al.,* 2006; Valori *et al.,* 2014; Philips and Rothstein 2014) thus, understanding the specific role of all CNS cells involved in ALS promises to be crucial in this complex scenario. Group I metabotropic glutamate receptors (mGluR1, mGluR5) represent the only excitatory mGluRs and are actively involved in the regulation of important cellular processes altered in ALS. These receptors have been found to be largely over-expressed in different experimental model of ALS (Aronica *et al.,* 2001; Berger *et al.,* 2012). We published number of data showing the presence of excessive Glu exocytosis in the spinal cord of mice expressing high copy number of human SOD1 carrying the G93A point mutation (SOD1^{G93A}). This abnormal Glu release was induced by different mechanisms, including the activation of presynaptic Group I metabotropic Glu receptors (Giribaldi *et al.,* 2013). As a matter of fact, in a very recent study we demonstrated that genetic knock-down of mGluR1, paralleled by unexpected reduction of mGluR5 expression, has a positive impact on disease progression and life span in a mouse model of ALS (Milanese *et al.,* 2014). Behavioral improvements was paralleled by MN preservation, reduced astrogliosis and microglia activation, normalization of oxidative stress markers, reduced mitochondrial damage and decrease of the excessive Glu-induced Glu release.
Following the same research hypothesis in the present work we investigated the role of mGluR5 in ALS. With this aim we generated two different SOD1^{G93A} mouse strains: SOD1^{G93A}mGluR5$^{+/-}$ and SOD1^{G93A}mGluR5$^{-/-}$. Half expression of mGluR5 in SOD1^{G93A} mice showed delayed pathology onset, measured as a shift in the body weight peak and a significantly prolonged life span. Surprisingly, these results were not accompanied by improved motor performances registered in behavioural tests. However we found a significant preservation of spinal motor neuron in the late phase of the disease and a normalized Glu-induce Glu release triggered by the activation of Group I metabotropic Glu receptors. When studying the SOD1^{G93A} mice knockout for mGluR5 (SOD1^{G93A} mGluR5$^{-/-}$) we got even more striking results in terms of prolonged survival probability. The life span amelioration was also accompanied by motor skills amelioration.
Overall, our findings demonstrate that both mGluR1 and mGluR5 down-regulation has a significant impact *in-vivo* on ALS clinical outcome and provide a rationale for pharmacological approaches based on the selective block of Group I mGluRs.

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