Partial deletion of mGluR1 receptors prolongs life span and ameliorates motor skills and biochemical and cellular parameters in a mouse model of experimental ALS

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Amyotrophic Lateral Sclerosis (ALS) is a chronic neuromuscular disorder reflecting progressive degeneration of upper and lower motor-neurons. Motor-neuron vulnerability has been ascribed to protein misfolding, mitochondrial dysfunction, oxidative damage, inflammation and glutamate-mediated excitotoxicity. High extracellular glutamate levels are present in ALS patients and animal models of the disease. Reduced astrocyte glutamate transport was suggested as a cause (Rothstein at al., 1995). Due to the complex interplay of multiple mechanisms in ALS, defects of transport may not be the only reason for excessive glutamate and excitotoxicity and other causes should be considered, including increase of neurotransmitter release (Milanese et al., 2011).

Our previous results have demonstrated the existence of excessive increase of Glu release in $SOD1^{G93A}$ mice mediated by Group I (mGlu1 and mGlu5) auto-receptor activation (Giribaldi et al., 2011), which may represent a cause of excessive Glu and of neurodegeneration.

To prove the impact of Group I metabotropic glutamate auto-receptor blockade in experimental ALS, we generated mice carrying half expression of mGlu1 receptors in the $SOD1^{G93A}$ background, by crossing ALS mutant mice with $Grm1^{+/-}$ mice, lacking mGlu1 receptors because of a spontaneous recessive mutation. In the same line we also generated mice carrying half expression of mGlu5 receptors, by crossing ALS mutant mice with $Grm5^{+/-}$ mice.

Survival, motor abilities, histology for MNs and mitocondrial damage, oxidative stress markers, biochemistry for astrogliosys and microglia activation, receptor expression, glutamate release

were investigated to assess the phenotype modi?cations in double mutants respect to $SOD1^{G93A}$ mice.

mGlu 1 receptor de?cient double mutants showed prolonged survival probability respect to single mutant $SOD1^{G93A}$ mice. Accordingly, slower disease progression and improved motor performances were observed. Histological studies showed higher number of Chat-positive MNs, reduced axonal degeneration and mitocondrial damage, reduced astrocyte and microglia activation, and reduced expression of oxidative stress markers in double mutant mice spinal cord at a late phase of the disease progression. Metallothioneins and glutathione S-transferase were studied as oxidative stress markers. Over expression of mGlu5 receptors and mGlu1 or mGlu5 receptor-induced abnormal release of Glu, observed in $SOD1^{G93A}$ mice, were reduced in double mutant animals. Also mGlu5 receptor-lacking $SOD1^{G93A}$ mice showed remarkable prolonged survival and phenotype amelioration.

To conclude, mGlu1 or mGlu5 receptor deletion has a signi?cant impact in-vivo on $SOD1^{G93A}$ mice pathology. These results would provide the rationale for pharmacological approaches to ALS by selectively blocking Group I metabotropic Glu receptors. With this aim pharmacological treatments with Group I receptor antagonists are in progress.

Rothstein et al. (1995). *Ann. Neurol.* 38(1), 73-84.
Milanese et al. (2011). *J. Neurochem.* 116(6), 1028-1042.
Giribaldi et al. (2012*). Neuropharmacol*. 66, 253-63.