Reducing mGlu5 receptors improves survival, symptoms and biological features in SOD1^{G93A} mice

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Amyotrophic lateral sclerosis (ALS) is a late-onset and fatal neurological disease characterized by degeneration of upper and lower motor neurons (MNs). The etiology of ALS remains unknown although glutamate(Glu)-mediated excitotoxicity plays a major role in neurodegeneration. In this scenario, Group I metabotropic Glu receptors (mGluR1, mGluR5), the only excitatory mGluRs, are involved in the regulation of important cellular processes altered in ALS and are over-expressed in different experimental models of the pathology. We have previously shown the presence of abnormal exocytotic release of Glu in the spinal cord of mice expressing high copy number of human SOD1 carrying the G93A point mutation (SOD1^{G93A}). Excessive Glu exocytosis can be triggered by different mechanisms, including activation of presynaptic mGluR1 and mGluR5. As a matter of fact, we have recently demonstrated that genetic knock-down of mGluR1 in SOD1^{G93A} mice had a positive impact on disease progression, life span and biological markers of ALS.

Following the same path, here we investigated the role of mGluR5 in ALS. We generated two different SOD1^{G93A} mouse strains with partial (SOD1^{G93A}mGluR5$^{+/-}$) and total (SOD1^{G93A}mGluR5$^{-/-)}$ receptor reduction. SOD1^{G93A}mGluR5$^{+/-}$ mice showed delayed pathology onset, extension of life span, preservation of spinal MNs and normalization of Glu release induced Group I mGluRs. Unexpectedly, these results were not accompanied by improved motor performances in behavioural tests. When studying SOD1^{G93A}mGluR5$^{-/-}$, we found a more conspicuous improvement of the pathology onset and of life span. Differently from SOD1^{G93A}mGluR5$^{-/-}$, these results were also accompanied by significant motor skill amelioration.

Overall, our findings demonstrate that mGluR5 down-regulation has a significant impact *in-vivo* on ALS clinical outcome and, together with previous data on mGluR1, provide a rationale for pharmacological approaches based on the selective block of Group I mGluRs.