Targeting Group I metabotropic glutamate receptors in ALS

M. Milanese, Department of Pharmacy Università di Genova, Genova Italy
T. Bonifacino, Department of Pharmacy Università di Genova, Genova Italy
L. Cattaneo, Department of Pharmacy Università di Genova, Genova Italy
E. Gallia, Department of Pharmacy Università di Genova, Genova Italy
A. Puliti, Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal and Child Health Istituto Giannina Gaslini, Genova Italy
M. Melone, Department of Experimental and Clinical Medicine Università Politecnica delle Marche, Ancona Italy
F. Provenzano, Department of Pharmacy Università di Genova, Genova Italy
C. Usai, Institute of Biophysics National Research Council (CNR), Genova Italy
F. Conti, Department of Experimental and Clinical Medicine Università Politecnica delle Marche, Ancona Italy
G. Bonanno, Department of Pharmacy and Centre of Excellence for Biomedical Research Università di Genova, Genova Italy

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by a selective death of upper and lower motor neurons (MNs). Although the etiology is not completely understood and has been ascribed to numerous causes, glutamate(Glu)-mediated excitotoxicity is still one major factor for MNs death (1,2). Several in-vitro and in-vivo studies show that MN damage in ALS is non-cell autonomous and likely depends on pathological changes in glial cells (3). At present there is no effective cure thus focused drug therapy are definitely needed. In this scenario the Group I metabotropic glutamate receptors (mGluR1 and mGluR5) may represent a potential target, since they have been found largely over-expressed and actively involved in the regulation of cellular processes altered in ALS (4,5,6). Indeed, we recently demonstrated that knocking-down mGluR1 significantly prolongs survival and ameliorates the clinical progression in the SOD1G93A mouse model of ALS (7).

Based on our results, we planned to investigate the role of mGluR5 in ALS. To this aim, we exploited two in-vivo experimental approaches testing the effects of: i) the genetic down-regulation of mGluR5 and ii) the pharmacological treatment with an mGluR5 negative allosteric modulator, in SOD1G93A mice.

For the first part of the project we generated double mutant mice carrying the SOD1G93A mutation and a partial mGluR5 deletion (SOD1G93AmGluR5+/-). The constitutive mGluR5 down regulation produced a shift of the pathology onset and a significant prolonged survival probability, measured by the Kaplan Meier analysis, in both male and female SOD1G93AmGluR5+/- vs. age matched SOD1G93A mice. The results were paralleled by a significant spinal cord MNs preservation and a decreased astrocyte and microglia activation in SOD1G93AGrm5-/+ mice. Halving the mGluR5 in the SOD1G93A background also normalized the elevated cytosolic [Ca2+]i and the excessive Glu release under basal or stimulated conditions (15 mM KCl or 0.3 μM 3,5-DHPG). Finally, we tested the motor skills and, unexpectedly, only male SOD1G93AmGluR5+/- mice showed improved motor performances vs. SOD1G93A mice.

In the second part of the project we translated the mGluR5 genetic down regulation into a pharmacological treatment with the orally bioavailable mGluR5 negative allosteric modulator CTEP (8). We treated 90 days old SOD1G93A mice and we analyzed the clinical progression and the survival probability, in comparison with vehicle treated SOD1G93A mice. We start our

pharmacological trial with the dose of 2mg/kg every 48 hs treating a total number of 30 animals with CTEP (15 male and 15 female) and 26 animals with the vehicle (16 male and 10 female). The results showed a slightly prolonged survival probability in the female group only accompanied by comparable amelioration of the clinical parameters. Subsequently, we performed a second trial with an higher dose of the drug (4 mg/kg every 24 hs; 15 male and 15 female for both CTEP and vehicle groups) that turned out to be more effective compared to the lower dose. In detail, the 4mg/kg treatment further increased the survival probability and ameliorated the clinical progression in female SOD1G93A mice; moreover showed a slight therapeutic effect also in male.

Overall, these data suggest that mgluR5 represent a potential target to counteract ALS. Although the results we obtained so far need to be confirmed and the underlying molecular mechanism further investigated, our pharmacological approach unveil a promising translational perspective in ALS.

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