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**Metabotropic glutamate receptor 5 as potential target to counteract amyotrophic lateral sclerosis**

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**A**myotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by motor neuron (MN) death, whose aetiology is not clear, although glutamate (Glu)-mediated excitotoxicity represents one major factor. Group I metabotropic glutamate receptors (mGluR1 and mGluR5) may be implicated in ALS, since they are largely over-expressed during disease progression and involved in altered cellular processes. In this scenario, we recently demonstrated that mGluR1 and mGluR5 at Glu synapses produces abnormal Glu release and that knocking-down mGluR1 in SOD1G93A mice significantly prolongs survival and ameliorates disease progression.

**Aim.** To study the function of mGluR5 in ALS, we investigated the effects of the genetic down-regulation of mGluR5 in SOD1G93A mice (SOD1G93AmGluR5<sup>+/-</sup>) or its ablation (SOD1G93AmGluR5<sup>-/-</sup>) and the pharmacological treatment of SOD1G93A mice with the mGluR5 NAM, CTEP.

**Results.** SOD1G93AmGluR5<sup>+/-</sup> mice showed delayed disease onset and prolonged survival probability, accompanied by spinal MN preservation, decreased astrocyte and microglia activation and normalization of the excessive cytosolic [Ca<sup>2+</sup>] I and Glu release. Unexpectedly, motor skills were improved in male SOD1G93AmGluR5<sup>+/-</sup> mice only. SOD1G93AmGluR5<sup>-/-</sup> presented a more evident amelioration of all disease features, including motor skills, both in males and females. Furthermore, we treated 90 days-old SOD1G93A mice with CTEP (2mg/kg/48hs; 4mg/kg/24hs) until death. The lower dose CTEP-treated-SOD1G93A mice showed a significant prolonged survival probability only in female mice, paralleled by improved clinical parameters. The higher dose CTEP produced a marked clinical amelioration, both in female and male SOD1G93A mice.

**Conclusion.** These results support the hypothesis that mGluR5 represents a useful target to counteract ALS.

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