Metabotropic glutamate receptor 5 as a potential target in ALS

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Introduction. Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by motor neuron (MN) death, whose aetiologyis not clear, although glutamate(Glu)-mediated excitotoxicity represents one major factor[1,2]. 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[3,4,5]. In this scenario, we recently demonstrated that mGluR1 and mGluR5 at Glu synapses produces abnormal Glu release[5] and that knocking-down mGluR1 in $SOD1^{G93A}$ mice significantly prolongs survival and ameliorates diseaseprogression[6].
Aim. To study the function of mGluR5 in ALS, we investigated the effects of the genetic down-regulation of mGluR5in $SOD1^{G93A}$ mice ($SOD1^{G93A}mGluR5^{+/-}$) or its ablation ($SOD1^{G93A}mGluR5^{-/-}$) and the pharmacological treatment of $SOD1^{G93A}$ mice with the mGluR5 NAM,CTEP[7].
Results. $SOD1^{G93A}mGluR5^{+/-}$ 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 $[Ca^{2+}]_i$ and Glu release. Unexpectedly, motor skills were improved in male $SOD1^{G93A}mGluR5^{+/-}$ mice only. $SOD1^{G93A}mGluR5^{-/-}$ presented a more evident amelioration of all disease features, including motor skills, both in males and females. Furthermore, we treated 90 days-old $SOD1^{G93A}$ mice with CTEP (2mg/kg/48hs;4mg/kg/24hs) until death. The lower dose CTEP-treated-$SOD1^{G93A}$ 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 $SOD1^{G93A}$ mice.
Conclusion. These results support the idea that mGluR5 represent a usefull target to counteract ALS.

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