The Modulation of Glutamate Release by Group I Metabotropic Glutamate Auto-receptors in ALS

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Amyotrophic Lateral Sclerosis (ALS) is a fatal neuromuscular disease characterized by muscle wasting, weakness and spasticity, reflecting a degeneration of upper and lower motor-neuron (MNs). The mechanisms of neuronal death are so obscure that efficacious therapies do not actually exist. It is well known that Glutamate(Glu)-mediated excitotoxicity plays a major role in the degeneration of motor neurons. According to our studies, we suggested that the high levels of synaptic Glu are due, not only to a reduced astrocytic Glu transport (Rothstein at al., 1995), but also to an abnormal Glu release (Milanese et al., 2011).

Recently, Group I metabotropic glutamate (mGlu1 and mGlu5) auto-receptors were described in rat cerebral cortex nerve endings (synaptosomes), the activation of which produced potentiation of Glu release (Musante et al., 2008). The aim of our work has been to investigate the modulation of Glu release by these auto-receptors in spinal cord of $SOD1^{G93A}$ mice, a widely used animal model of ALS (Gurney et al., 1994).

Exposure of spinal cord synaptosomes to increasing concentrations of 3,5-DHPG, mGluR1/5 agonist, produced distinct effects in $SOD1^{G93A}$ and control mice: concentration above 0.3 μM stimulated the basal release of [^{3}H]D-Aspartate, an analogus not-metabolizable of Glu, both in control and $SOD1^{G93A}$ mice. At variance, concentrations of 3,5-DHPG equal to or lower than 0.3 μM increased [^{3}H]D-Aspartate release in $SOD1^{G93A}$ mice only. Experiments with selective mGluR1 or mGluR5 antagonists indicated that both high and low potency effects of 3,5-DHPG involved mGluR1 and mGluR5 activation. High 3,5-DHPG concentrations increased IP3 in both mouse strains, whereas low 3,5-DHPG induced IP3 formation in $SOD1^{G93A}$ mice only. Release experiments confirmed that 3,5-DHPG elicited [^{3}H]D-Aspartate exocytosis involving intra-terminal Ca^{2+} release through IP3-sensitive channels. Moreover, confocal microscopy indicated the co-existence of both receptors in the same nerve terminals and western blot analysis showed an higher expression of mGlu5 receptors in $SOD1^{G93A}$ mice.

We can conclude that the activation of both mGlu1 and mGlu5 receptors produced abnormal Glu release in the spinal cord of $SOD1^{G93A}$ mice, an event possibly linked to the 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 mGluR antagonists are in progress.

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