Gender-dependent effect of P2X7 antagonism in a mouse model of ALS

C. Cervetto[1,2], D. Frattaroli[1], G. Maura[1,2], M. Marcoli[1,2]

[1]Dept. of Pharmacy, Pharmacology and Toxicology Section, University of Genoa, Italy; and [2]Center of Excellence for Biomedical Research CEBR, University of Genoa, Italy

Amyotrophic lateral sclerosis (ALS) is a currently untreatable disease, characterized by selective motor neuron degeneration; the incidence and prevalence of ALS are greater in men than in women. Although some important mechanisms that might contribute to the death of motor neurons have been identified, the mechanisms underlying disease pathophysiology are still uncertain. In particular, the mechanisms underlying the role of gender in ALS remain only partially understood. Studying transgenic mice with superoxide dismutase 1 gene mutations, widely used as model for ALS, may provide a better understanding of pathogenic mechanisms and of toxicity towards motor neurons, also possibly helping to understand whether treatments for ALS should take into account sexual dimorphism.

Purinergic signalling has emerged as playing primary roles in neuroinflammatory mechanism activation that underlie neurodegenerative diseases including multiple sclerosis, Alzheimer's and Huntington's diseases and ALS. The ATP-gated ionotropic P2X7 receptor, initially discovered on cells of haematopoietic lineage, was subsequently described in the nervous system. The receptor is localized on microglia, astrocytes, oligodendrocytes and Schwann cells, and on neurons. It became apparent that the receptor can be associated with the regulation of neuron death and survival, and it may be involved in the pathogenesis of disorders involving dysregulation of glutamatergic transmission and activation of neuroinflammatory cascade involving microglial and astrocyte activation. In particular, activation or overexpression of P2X7 receptor was found related to motor neuron toxicity and to motor neuron injury; blockade of the P2X7 receptor has neuroprotective effects in animal models of motor neuron injury.

The aim of the work was 1) investigating on gender-dependence of disease progression in the standard model for ALS – a transgenic mice carrying a high copy number of a transgene encoding a variant of human superoxide dismutase 1 with a G93A mutation (Gly93Ala substitution), SOD1/G93A mice, - and 2) assessing if a P2X7 receptor antagonist treatment should take into account sexual dimorphism.

We evaluated if gender affect the disease course, the motor performance, the weight loss and the lifespan in mice overexpressing mutant superoxide dismutase 1. We measured motor impairment, motor strength and coordination by rotarod and grip strength testing. Further, we assessed if a treatment with the P2X7 receptor antagonist Brilliant Blue G – a dye that can cross the blood–brain barrier, has low toxicity, and has exhibited therapeutic effects in animal models of neurodegenerative diseases - impact on the disease progression, in male and female ALS mice.

We found that 1) the onset and the disease progression, and the survival were dependent on gender: SOD1/G93A male performed worst than female, lost body weight and died before; 2) treatment with the P2X7 receptor antagonist Brilliant Blue G ameliorated the disease progression. The treatment effect was gender-dependent: amelioration was greater in male than in female.

In conclusions, we suggest that the drug treatment effectiveness may depend on gender; sexual dimorphism should be considered when investigating on ALS treatment efficacy in the ALS animal model. Our findings also point on the potential relevance of P2X7 receptor antagonism for ALS treatment, and highlight the importance of adopting a sex-specific approach to searching for treatment of ALS.

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