RESEARCH ARTICLE

Spinal cord pathology is ameliorated by P2X7 antagonism in a SOD1-mutant mouse model of amyotrophic lateral sclerosis

Savina Apolloni, Susanna Amadio, Chiara Parisi, Alessandra Matteucci, Rosa L. Potenza, Monica Armida, Patrizia Popoli, Nadia D'Ambrosi and Cinzia Volonté

ABSTRACT

In recent years there has been an increasing awareness of the role of P2X7, a receptor for extracellular ATP, in modulating physiopathological mechanisms in the central nervous system. In particular, P2X7 has been shown to be implicated in neuropsychiatry, chronic pain, neurodegeneration and neuroinflammation. Remarkably, P2X7 has also been shown to be a 'gene modifier' in amyotrophic lateral sclerosis (ALS): the receptor is upregulated in spinal cord microglia in human and rat at advanced stages of the disease; *in vitro*, activation of P2X7 exacerbates pro-inflammatory responses in microglia that have an ALS phenotype, as well as toxicity towards neuronal cells. Despite this detrimental *in vitro* role of P2X7, in SOD1-G93A mice lacking P2X7, the clinical onset of ALS was significantly accelerated and disease progression worsened, thus indicating that the receptor might have some beneficial effects, at least at certain stages of disease. In order to clarify this dual action of P2X7 in ALS pathogenesis, in the present work we used the antagonist Brilliant Blue G (BBG), a blood-brain barrier permeable and safe drug that has already been proven to reduce neuroinflammation in traumatic brain injury, cerebral ischemia-reperfusion, neuropathic pain and experimental autoimmune encephalitis. We tested BBG in the SOD1-G93A ALS mouse model at asymptomatic, pre-symptomatic and late pre-symptomatic phases of disease. BBG at late pre-onset significantly enhanced motor neuron survival and reduced microgliosis in lumbar spinal cord, modulating inflammatory markers such as NF-κB, NADPH oxidase 2, interleukin-1β, interleukin-10 and brain-derived neurotrophic factor. This was accompanied by delayed onset and improved general conditions and motor performance, in both male and female mice, although survival appeared unaffected. Our results prove the twofold role of P2X7 in the course of ALS and establish that P2X7 modulation might represent a promising therapeutic strategy by interfering with the neuroinflammatory component of the disease.