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Excessive glutamate release and undelying synaptic mechanisms in a mouse model of amyotrophic lateral sclerosis.

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Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease, characterized by upper and lower motor neuron degeneration. Glutamate(Glu)-mediated excitotoxicity plays a major role in cell death and Glu has been found elevated in serum of patients and animal models of ALS. The aim of this research was to investigate whether the augmented extracellular Glu can be sustained by alteration of its release. Glu release was studied from purified spinal cord synaptosomes of SOD1G93A mice at the early and the late phases of the disease (4 and 17 weeks of life, respectively). Both the spontaneous and the stimulus-evoked exocytotic Glu release were increased at the two stages studied. We also measured the expression/activation state of a number of pre-synaptic proteins involved in neurotransmitter release: few of them were found modified and synaptotagmin and actin resulted over-expressed in both 4 and 17 week-old mice. Increased pre-synaptic Ca²⁺ levels, over-activation of calcium/calmodulin-dependent kinase-II and ERK/MAP kinases correlate with hyper-phosphorylation of synapsin-I at both stages. In line with these findings, Glu exocytosis was paralleled by the increase of the readily releasable pool of vesicles and prevented by blocking synapsin-I phosphorylation, using specific antibodies. Our results highlight that abnormal glutamate release is present in the spinal cord of SOD1G93A mice at the pre-symptomatic and late stage of the disease, an event accompanied by marked plastic changes of specific pre-synaptic mechanisms supporting exocytosis, that in turn may represent targets to diminish excitotoxicity in ALS. The precociousness of this phenomenon may imply that it represents a cause rather than a consequence of the neuronal damage during disease progression.

Biography

Tiziana Bonifacino PhD, is an Assistant Professor at the Department of Pharmacy, University of Genoa, Italy. She got the degree in Chemistry and Pharmaceutical Technology (honors) in 2007 and the PhD in Neurochemistry and Neurobiology in 2011. The present scientific interests are related to neuronal transmission in the CNS and are focused on the cellular and molecular mechanisms of neurotransmitter release and receptor activity in physiological and pathological conditions, such as amyotrophic lateral sclerosis. She has established several scientific collaborations with national and international institutions. She has published 32 publications (25 papers, 6 abstract on journals and 1 graphical abstract) in peer-reviewed journals.

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