IJAE
Vol. 118, n. 2 (Supplement): 95, 2013
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Sub-cellular motor neuron analysis in a model of spinal muscle atrophy

Federica Fulceri[1], Cristina Demi[1], Marco Gesi[1], Paola Parlanti[1], Francesca Biagioni[2], Antuela Matarangasi[1], Paola Soldani[1] and Antonio Paparelli[1]

[1] Human Anatomy-Department of Translational Research and new Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy
[2] IRCCS Neuromed, Pozzilli (IS), Italy

Spinal muscular atrophy (SMA) is a neurogenetic autosomal recessive disorder characterized by degeneration of lower motor neurons associated with muscle atrophy and paralysis.

The disease course including onset and severity depends by reduced amounts of the survival motor neuron (SMN) protein. Such a protein is increased when the enzyme glycogen synthase kinase-3beta (GSK3beta) is inhibited.

In the present study we used a knockout double transgenic mouse (Smn−/−; SMN1A2G; SMN2) modelling SMAIII to dissect the spinal cord pathology at ultrastructural analysis at prolonged survival time (18 months). We analysed the subcellular structure of spinal cord motor neurons both in baseline conditions and following the administration of a GSK3beta inhibitor.

We found that motor neurons increased their diameter confirming our previous light microscopy data. The amount of immunogold labelled SMN particles was dramatically reduced in the whole cell body incuding nucleus and cytoplasm. Remarkably, at nuclear level we could detect marked reduction of the SMN protein with Cajal-like bodies thus mimicking the human disease. In mice receiving long-term lithium administration the level of the SMN protein were massively increase way more than other SMAIII mice and significantly exceeding the levels counted in controls. When compared with control mice administered long-term lithium SMN levels in SMA III mice were overlapping with healthy animals, at large. The effects of lithium on ultrastructural morphology of motor neurons extended to the preservation of mitochondrial compartment which was slightly affected in motor neurons from SMA III mice. These data confirm the essential role of GSK3beta inhibition in increasing the amount of the SMN protein and provide a novel action for an old drug which increases SMN level exceeding any other compound tested so far in this motor neuron pathology. At the same time the beneficial effects of lithium on mitochondrial morphology are confirmed.

As an appendix to the present study we wish to mention the ubiquitous nature of these effects which were replicated in non-motor neuron cell lines. Apart from the significance in cell biology this latter observation provide the basis to analyze the effects of a lithium treatment on affected patients using peripheral or skin-derived cell cultures.

This work was supported by an educational grant from CUCCS

References

[1] Fornai et al. (2008) Lithium delays progression of amyotrophic lateral sclerosis. Proc Natl Acad Sci USA 105(6): 2052-2057.
[2] Struewing et al. (2007) Lithium increases PGC-1alpha expression and mitochondrial biogenesis in primary bovine aortic endothelial cells. FEBS J 274(11): 2749-2765.

Key words

Spinal Muscular Atrophy, Survival motor neuron protein, Motor neurons, Transmission Electron Microscopy, Lithium.