

Lithium protects motor neurons at prolonged time intervals in a single knock out double transgenic mouse model of spinal muscle atrophy

Federica Fulceri¹, Mariangela Guagnozzi¹, Antuela Matarangasi¹, Livia Pasquali², Gabriele Siciliano² and Antonio Paparelli¹

¹ Department of Human Morphology and Applied Biology, University of Pisa, Pisa, Italy

² Department of Neuroscience, Clinical Neurology, University of Pisa, Pisa, Italy

In the present study, we profited from a slow progressive model of motor neuron death in a knock out double transgenic mouse model (SMN2+/+; Smn-/-; SMN1A2G+/-) of Spinal Muscle Atrophy type III (SMA III) to evaluate the protective effects of lithium. In detail, disease progression was evaluated up to 535 days of age and lithium was administered for 455 days. During this time interval motor behaviour was constantly monitored. The spinal cords were analyzed both at light and electron microscopy. The levels of the survival motor neuron protein (SMN) were quantified by Western blotting cord homogenates.

We found that lithium was effective to prevent motor decay and fully protected motor neuron loss as well as motor neuron size variations. In the anterior white matter lithium induced a decrease in the radial-like gliosis. These findings were substantiated by an in depth analysis at electron microscopy.

These effects were accompanied by a dramatic increase of the SMN protein measured by immunoblotting the whole spinal cord. When observed in situ SMN appeared to be localized in various cell types. When counted by ultrastructural morphometry motor neuron levels of SMN were dramatically increased under the influence of lithium.

Interestingly, the effects induced by lithium in the spinal cord and specifically within motor neurons were also described in wild types (in the absence of motor neuron degeneration).

These data demonstrate that lithium might be effective in counteracting the disease process occurring in spinal muscle atrophy while it appears to be by far the most effective compound to increase the levels of the key protein SMN. These effects might be due both to the inhibition of GSK3beta and inositol monophosphate phosphatase thus influencing in turn the wnt and the autophagy pathways.

Keywords: SMA, SMN, lithium, motor neuron degeneration.