IJAE
Vol. 117, n. 2 (Supplement): 36, 2012
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Morphofunctional characterization of peripheral nerve damage and recovery in sphyngomielinase deficient mice

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Mutation of the acid sphingomyelinase (ASM) gene and its reduced enzymatic activity is the main cause of the Type A Niemann-Pick disease. Recent advances demonstrated that ASM is necessary and sufficient to control the formation and release of microvesicles containing the proinflammatory cytokine interleukin-1β (IL-1β) by glial cells [1]. Since IL-1β modulates the events caused by nerve damage and repair and seems to act as a neuro-modulator between activated glia and neurons [2], the control of its production and secretion might represent a new strategy in nerve regeneration and in the control of neuropathic pain.

In this study we used a well-characterized ASM knockout mouse (ASMKO, [3]) to evaluate, through a multimodal approach, the onset and the course of the morphological and functional nerve damage and of neuropathic pain after sciatic nerve crush.

Adult (1 and 5 month-old) male ASMKO and age-matched wild-type (WT) mice underwent sciatic nerve crush lesion. Nerve conduction velocity (NCV), walking track analysis followed by ultra-structural and morphometric analysis of sciatic nerves were performed to evaluate the features of nerve damage. Thermal (Plantar test) and mechanical sensitivity (Dynamic Plantar Aesthesiometer apparatus) were used to measure the severity of neuropathic pain. Moreover, the rotarod test completed the analysis as an indicator of motor impairment.

One or two months after the nerve crush motor functional recovery was similar in WT and KO mice and the NCV measures performed in the sciatic nerve demonstrated a moderate and progressive improvement of nerve function. The results of the morphological examination confirmed the expected course of nerve recovery, but also demonstrated defective nerve regeneration, particularly evident in older, but already present in younger ASMKO mice. Behavioral tests suggested that the mutated phenotype in ASMKO might have an effect on the onset and development of mechanical and thermal hyperalgesia after nerve crush in both 1 - month and 5 - months - old groups.

In conclusion, these data suggest a possible role for ASM-related microvesicles in nerve regeneration and suggest that targeting the IL-1β production and release may represent a new therapeutic strategy for the treatment of nerve damage and neuropathic pain.

References

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Keywords: Sciatic nerve crush, IL-1β, ASM knockout mice, neuropathic pain.