

## INCREASED CHOLINERGIC TONE MIMICS THE EFFECTS OF CHRONIC TREATMENT WITH AChE INHIBITORS AND IS ASSOCIATED WITH NEUROMUSCULAR DEGENERATION IN MICE

MAGALHÃES-GOMES, Matheus Proença Simão<sup>a,e\*</sup>; VAUGHAN, Sydney K<sup>g</sup>; FURTADO, Isadora<sup>a</sup>; RAMOS, Emylle Karoline<sup>c</sup>; VALADAO, Priscila Aparecida Costa<sup>a</sup>; TEIXEIRA, Vanessa Pereira<sup>b</sup>; PRADO, Marco Antônio Máximo<sup>d</sup>; PRADO, Vânia Ferreira<sup>d</sup>; GUATIMOSIM, Sílvia<sup>b</sup>; CAVALCANTE, Walter Garrido<sup>c</sup>; VALDEZ, Gregorio; GUATIMOSIM, Cristina.

a Departamento de Morfologia, ICB, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil

b Departamento de Fisiologia e Biofísica, ICB, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil

c Departamento de Farmacologia, ICB, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil

d Robarts Research Institute and Department of Physiology and Pharmacology and Anatomy & Cell Biology, University of Western Ontario, London, ON, Canada

e Departamento de Medicina, Faculdade Ciências Médicas de Minas Gerais, FCMMG, Belo Horizonte, MG, Brazil

f Brown University Department of Molecular Biology, Cell Biology and Biochemistry, Providence, Rhode Island, USA.

g Mayo Clinic, Jacksonville, Florida, USA.

\*Corresponding author: [matheus.gomes@cienciasmedicasmg.edu.br](mailto:matheus.gomes@cienciasmedicasmg.edu.br)

**INTRODUCTION** It is known that several neuromuscular diseases like myasthenia gravis (MG) are treated with cholinesterase inhibitors (AChEi) to increase acetylcholine (ACh) availability at the synaptic cleft and improve neuromuscular function. However, chronic treatment with these drugs can result in adverse effects in neuromuscular junctions (NMJs) structure and desensitization of nicotinic receptors (AChRs), worsening patients' symptoms. **OBJECTIVES** Thus, in this work, we investigated the effects of increasing cholinergic tone on neuromuscular function and structure. **METHODS** We used an engineered mouse line [(called SuperVACHT (SVT)] that expresses 20x more copies of the Vesicular Acetylcholine Transporter (VACHT), which is a vital protein that fill in synaptic vesicles (SVs) with ACh, resulting in more neurotransmitters being released at the synaptic cleft. Therefore, we performed a morpho-functional analysis of the components of the motor units (M.U) from these mice. **RESULTS** We showed that compared to control, SVT mice were more active in locomotor activities in relation to control, however, structurally, they presented reduction of the diameter of  $\alpha$ -motoneurons from the lumbar spinal cord, smaller and denervated NMJs of the extensor digitorum longus (EDL), reduction of the cross-sectional area (CSA) of the muscles fibers from EDL and Soleus, together with altered expression of myosin heavy chain isoforms showing changes with the biochemical profile of these muscles. In addition, we observed that the soleus muscle was more prone to fatigue in the SVT mice group. **CONCLUSION** Increased cholinergic tone induces alterations with the M.U, showing that chronic use of AChEi must be closely monitored by physicians.

**Key words:** Acetylcholine. Cholinesterase Inhibitors. Neuromuscular Junction Diseases.