GROWTH HORMONE SECRETAGOGUES PREVENT CISPLATIN-INDUCED MUSCLE WASTING: CHARACTERIZATION OF MULTIPLE MECHANISMS INVOLVING SARCOPLASMIC RETICULUM AND MITOCHONDRIA

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Cachexia affects the majority of cancer patients, with currently no effective pharmacological treatment. The most important clinical feature of cachexia is the excessive wasting of skeletal muscle mass. Cisplatin, a cytotoxic agent widely used in cancer treatment, also induces cachexia. Using a rat model of cisplatin-induced cachexia, we recently demonstrated (Conte et al., 2017) that, coherently with the loss of skeletal muscle mass, cachectic rats showed the alteration of several in vivo and ex vivo outcomes related to a decline of muscle performance. Furthermore, according to the multiple actions proposed for ghrelin and growth hormone secretagogues (GHS) (Anderson et al., 2017), we also demonstrated that administration of JMV2894, a novel peptidomimetic GHS, and hexarelin, a well-known synthetic hexapeptide, antagonized the cisplatin-induced muscle weakness (Conte et al., 2017). Muscle wasting in cachexia is likely multifactorial and the underlying mechanism remain largely unknown. Mitochondria and sarcopalsmic reticulum (SR) are very important for the correct skeletal muscle function and an intimate association between these organelles, resulting in a symbiotic signaling interaction, has been proposed (Rossi et al., 2009; Franzini-Armstrong and Boncompagni 2011). By a multidisciplinary approach, ranging from cytofluorometry to biochemistry and gene expression analysis, the objectives of this study were to establish the molecular origins of chemotherapy-induced myopathy with a focus on SR and mitochondria in fast-twitch muscles (exstensor digitorum longus, EDL; tibilias anterior, TA) of adult rats with cisplatin-induced cachexia (1 mg/Kg, ip once daily, for 3 days) and to establish the potential beneficial effects of hexarelin and JMV2894 at this level. We showed that, besides a significant reduction of muscle weight together with an upregulation of atrogin1/Murf-1 genes, all indexes of muscle atrophy, fura-2 load cachetic EDL fibers are characterized by a 50% reduction of the amplitude of the caffeine-induced calcium transient together with a decrease of ryanodine receptor 1 (RyR1) gene expression. Furthermore, we found that cisplatin treatment caused in TA muscle a decrease in mitochondrial biogenesis (PGC-1□, TFAM, mtDNA), mitochondrial mass (Citrate synthase activity) and fusion index (MFN2, Drp1), with an increase in autophagy-related gene expression (AKT/FoxO pathway, Atg1, beclin1) and enhanced ROS production (PRXIII, MnSOD). Importantly, administration of JMV2894 or hexarelin (320 □g/Kg and 160 □g/Kg respectively, ip, b.i.d, for 5 days) was capable to antagonize these chemotherapy-induced SR and mitochondrial dysfunctions by both common as well as drug-specific mechanisms of action. All our findings support the idea that the occurrence of muscle weakness that we observed in vivo after cisplatin administration (Conte et al., 2017) may result from a combined effect of mitochondria and SR dysfunctions and that the prevention of these changes by hexarelin and JMV2894 could contribute to preserve in vivo muscle function. Thus, our findings reveal a key-role played by SR and mitochondria in the mechanism responsible for GHS

beneficial effects in skeletal muscle, strongly indicating that targeting these organelles might be a promising area of research in developing therapeutic strategies to prevent or limit muscle wasting in cachexia.

Anderson et al. Curr Oncol Rep. 19: 3, 2017.

Conte et al. J Cachexia Sarcopenia Muscle 2017 in press

Franzini-Armstrong & Boncompagni. J Biomed Biotechnol. 2011:830573, 2011.

Rossi et al. Exerc Sport Sci Rev. 37: 29-35, 2009.