

Growth hormone secretagogues administration prevents skeletal muscle calcium homeostasis alteration in an animal model of cachexia

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Cachexia is a wasting condition associated with cancer types and, at the same time, is a serious and dose-limiting effect of cancer chemotherapy. Skeletal muscle loss is the main characteristic of cachexia and the primary cause of function impairment, fatigue and respiratory complications. Calcium-dependent signaling pathways are believed to play an important role in skeletal muscle decline observed in cachexia, but whether intracellular calcium homeostasis is affected in this situation remains obscure (Argiles et al., 2014). Growth hormone secretagogues (GHS), ghrelin mimetics known to increase appetite, lean and fat mass, are being developed as a therapeutic option for cancer cachexia syndrome (Argiles and Stemmler, 2013). We have previously demonstrated that GHS can differently affect skeletal muscle fibers depending on their molecular structure through regulation of intracellular calcium (Liantonio et al., 2013). By a multidisciplinary approach, the objectives of this study were to characterize the calcium homeostasis in fast-twitch EDL muscle of adult rats with cisplatin-induced cachexia (1 mg/Kg, ip once daily, for 3 days) and to establish the potential beneficial effects of GHS in this setting. We showed that besides a significant reduction of the muscle weight and fiber diameter, indexes of an overt muscle atrophy, fura-2 load cachetic EDL fibers are characterized by a significant 56% increase of resting intracellular calcium, $[Ca^{2+}]_i$, compared to control rats. Moreover the amplitude of the calcium transient induced by caffeine and depolarizing high potassium solution was significantly reduced in cisplatin-treated rats. Importantly, changes of some calcium-dependent functional outcomes, such as an increase of the latency of the action potential and a decrease of resting chloride conductance, also occurred in cachetic EDL muscles, thus indicating that the cachexia-induced alteration of calcium homeostasis influences muscle functionality. To gain insight into the molecular mechanism responsible for calcium dysregulation, by using real time PCR analysis, we investigated the expression levels of some genes related to muscle wasting and calcium machinery. We find that in cachetic muscles, in line with the atrophic muscle condition, Murf-1 and atrogen-1 transcripts associated with the ubiquitin-proteasome system, were significantly increased, while according to the calcium alteration observed, ryanodine receptor (RyR1) and dihydropyridine receptor (DHPR) resulted downregulated. Importantly, administration of hexarelin or JMV2894 (160 µg/Kg and 320 µg/Kg respectively, ip, b.i.d, for 5 days), efficaciously prevents cisplatin-induced muscle weight loss and $[Ca^{2+}]_i$ increase as well as ameliorates the related calcium-dependent functional parameters. Hexarelin fully restored the gene expression of Murf-1 and DHPR, while JMV2894 resulted efficacious in recovery gene expression alteration of DHPR and RyR1 but it was not able to prevent the cisplatin-induced increase of Murf-1. The differential effect mediated by the two GHS on the gene expression profile, indicate that they could produce beneficial effects on calcium homeostasis through different mechanism of action. In conclusion, our findings provide the first direct evidence of a calcium homeostasis dysregulation in an experimental model of cachexia gaining insight into the etiopathogenesis of this form of muscle wasting. Furthermore, our demonstration that GHS administration efficaciously prevents cisplatin-induced calcium homeostasis alteration contributes to the elucidation of the mechanism of action through which GHS could potentially ameliorate chemotherapy-associated cachexia.

Argiles et al., Nat Rev Cancer, 14(11): 754-62, 2014

Argiles and Stemmler, Expert Opin Biol Ther, 13(1): 67-76, 2013

Liantonio et al., Endocrinology, 154(10): 3764-75, 2013