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Therapeutic option by synergistic administration of the β-hydroxy-β-methyl butyrate and R(+) Lipoic Acid in a cellular model of dexamethasone-dependent sarcopenia

Alessandra Pacini[1], Lorenzo Di Cesare Mannelli[2], Barbara Tenci[2], Mario Maresca[2], Claudio Celi[3], Roberto Gabriele[3], Carla Ghelardini[2]

[1] Dipartimento di Medicina Sperimentale e Clinica (DMSC) - Sezione Anatomia, Università degli Studi di Firenze, Firenze, Italy - [2] Dipartimento di Neuroscienze, Psicologia, Area del Farmaco e Salute del Bambino (NEUROFARBA) - Sezione Farmacologia e Tossicologia, Università degli Studi di Firenze, Firenze, Italy - [3] MDM S.P.A., Monza, Italy

The decline of muscle mass and strength, known as sarcopenia, is a clinical problem associated with osteo-articular diseases, muscle disuse, cancer, renal failure, postmemenopause, age and corticosteroid treatments [1,2]. In this scenario, alterations in mitochondrial function [3] and accelerated apoptosis in skeletal muscle [4] are considered a major factor underlying sarcopenia and muscle atrophy. These evidences suggests that targeting myonuclear apoptosis as well as reducing the oxidative stress might provide novel and effective therapeutic tools to combat sarcopenia. Alpha-lipoic acid (1,2-dithiolane-3-pentanoic acid), is a natural antioxidant with two optical isomers of which the (+)- possess a more pronounced effect (R (+) LA) [7]. Beta-hydroxy-beta-methylbutyrate (HMB), a leucine catabolite, has been shown to prevent muscle damage directly enhancing myogenic cells (satellite cells) proliferation and attenuating apoptosis [8].

Aim of the present research was the evaluation of the pharmacological profile of the HMB associated with the natural R(+)LA in a cellular model of muscle wasting.

Material and Methods. C2C12 cell line was used as myoblasts or differentiated in miotubes by 7 day culture with 2% horse serum. Cell damage was induced by dexamethasone. Results. Dexamethasone toxicity was evaluated measuring cell viability (MTT assay) and apoptosis induction (caspase 3 activity) after 24h and 48h incubation of myoblasts with the glucocorticoid (0.01–300 μM concentration range). One μM dexamethasone (48h) decreased cell viability by about 50% and increased caspase 3 activity by 80%. R(+)LA (100 and 300 μM) or HMB (1 and 3 mM) significantly prevented dexamethasone-induced cell mortality; the efficacy was improved when 100 μM R(+)LA was combined with 1mM HMB, demonstrating the synergistic effect of R(+)LA and HMB in preventing cell mortality and caspase 3 activation. Similarly, the evaluation of dexamethasone evoked $O_2^{-\cdot}$ production and protein carbonylation demonstrated the efficacy of the combination of R(+)LA with HMB. In the early phase of myotube differentiation (72h) the combination of R(+)LA and HMB preserved the number of myogenin-positive cells as well as in the later (7 days) phase of differentiation the dexamethasone-dependent damage (evaluated as cell diameter and percentage of multinucleated cells).

These data offer a rational to candidate the mixture as a therapeutic option for sarcopenia treatment.

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Keywords

Sarcopenia; β-Hydroxy-β-methyl butyrate; R(+) Lipoic Acid.

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