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THE EFFECTS OF METFORMIN-LEUCINE DUAL THERAPY ON MUSCLE RECOVERY FOLLOWING INACTIVITY IN AGED MICE

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Intro: Aging is part of the normal process of living, though as individuals age they often experience negative consequences such as increased muscle degradation and decreased muscle repair capability. With increased muscle degradation comes increased likelihood of fall and injury, which frequently leads to hospitalization or extended periods of inactivity. Ultimately this degradation puts older adults (age 65+) at risk of developing metabolic diseases, experiencing prolonged physical decline, and increases their risk of mortality. Metformin, a drug currently used to treat type 2 diabetes, is of interest to combat many age-related diseases such as cancer, dimension, and heart disease, though the drug's effects on muscle recovery in aged populations has not been studied. We hypothesized that a combination treatment of metformin with leucine, an amino acid that is linked to muscle protein synthesis and skeletal muscle regrowth, would improve skeletal muscle regenerative capacity in aged mice after periods of disuse.

Purpose: To characterize the cellular and molecular effects of a Met + Leu combined therapy on muscle regrowth after an inactivity event.

Methods: Mice were broken into four groups: a baseline ambulatory group, a 14-day hind limb unloading (HU) group, and 14-day hind limb unloading followed by 7-day reloading (7dRL) group, and a 14-day hind limb unloading followed by 14-day reloading group (14dRL). Mice were given a metformin + leucine (Met + Leu) combination dissolved in drinking water through the inactivity and recovery periods. At the time of sacrifice the gastrocnemius muscles were dissected and analyzed.

Results: Following HU, gastrocnemius muscle mass decreased in control and Met+ Leu mice when compared to ambulatory baseline. Following HU the Met + Leu mice reported an increase in Pax 7+ satellite cells per muscle fiber ($P < 0.05$) and trended to increase central nuclei ($P > 0.05$) – a marker of muscle regeneration. Central nuclei were elevated in the Met + Leu mice at 7dRL compared to control ($P < 0.05$) and ambulatory baseline ($P < 0.05$), and returned to ambulatory baseline levels by 14dRL, though the central nuclei still trended to be higher ($P > 0.05$). The total collagen IV content following HU was reduced in Met + Leu mice compared to control, 7dRL, and 14dRL ($P < 0.05$). The ratio of B-CHP to collagen IV – an indicator of collagen turnover – was increased following HU in Met + Leu, 7dRL, and 14dRL mice ($P < 0.05$). Met + Leu mice had increased collagen turnover at 14dRL ($P < 0.05$) and trended to increase collagen turnover compared to ambulatory baseline at 7dRL ($P > 0.05$). We conclude that a metformin + leucine treatment allows for faster, high quality muscle recovery after periods of inactivity through an increased regenerative potential and decrease in fibrosis.