



THE EFFECTS OF METFORMIN ON RECOVERY OF MUSCLE MASS AND MITOCHONDRIAL FUNCTION IN OLDER HINDLIMB UNLOADED MICE

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Intro: Aging results in impaired recovery of muscle mass and function after periods of disuse. Inadequate restoration of muscle loss can lead to weakness, decreased physical function, and mitochondrial dysfunction. Evidence suggests that the widely prescribed FDA approved insulin sensitizer metformin, may enhance recovery of muscle after disuse-induced atrophy.

Purpose: To compare muscle mass and mitochondrial function between mice provided with metformin vs placebo after 7 days of recovery from hindlimb unloading (HU).

Methods: A cohort of young (3 mo, n=6) and old (24 mo, n=8) mice were subjected to 14 days of HU via tail suspension, followed by 7 day return to normal ambulation. Muscle weights were measured (absolute and relative to body weight) to determine aged-related impairments in recovery. A follow-up study was performed on old only mice, where one group was provided with metformin (n=5) (vs placebo, n=5) in their drinking water for the entire 21 days (14d hindlimb unloading+ 7d recovery). Muscle mass and mitochondrial function (red and white gastrocnemius separately) using the Oxygraph-2K (Oroboros Instruments, Austria) were measured. Molecular targets of metformin (AMPK α and Acetyl-CoA carboxylase) were analyzed with western blotting.

Results: Recovery of gastroc muscle mass was impaired in both metformin and placebo aged mice as compared to young. Direct comparison between metformin and placebo groups demonstrated a trend towards improved recovery of the gastroc muscle mass with metformin treatment (absolute: $P=0.0999$, relative: $P=0.1189$). Mitochondrial respiration for all complexes (per mg dry muscle) were different between red and white gastroc however no differences were found in mitochondrial function nor cellular signaling with metformin vs placebo. Interestingly, absolute gastroc weight and white gastroc complex 1&2 coupled respiration was positively correlated ($R^2=0.0325$, $P=0.0419$). Conclusion: Metformin may assist in recovery of gastroc muscle mass in aged mice, however metformin may not influence mitochondrial function nor AMPK α and ACC signaling during 7d of recovery from hindlimb unloading. Recovery of muscle mass is associated with greater complex 1&2 respiration in the white gastroc.