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BASICS IN AGING

WHAT IS THE IMPACT OF LATE-LIFE RAPAMYCIN ON EXERCISE ADAPTATIONS IN OLDER MICE?

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Exercise is associated with decreased risk of multi-morbidity and mortality while rapamycin can extend lifespan and decrease age-related pathologies in model systems. An increasing number of physically active older adults are now taking rapamycin off label with the goal of further extending healthspan than either intervention alone (1). However, there is a paucity of data to understand whether combining these treatments can have positive or detrimental effects on fundamental mechanisms of aging, metabolism, and healthy longevity (2). Despite the lifespan extending effects, frequent rapamycin dosing disrupts metabolic health during sedentary conditions (3) and restricts skeletal muscle hypertrophy after electrical stimulation which would seemingly appear contrary to healthy longevity. Intermittent once-weekly rapamycin can also confer lifespan extension while alleviating metabolic disruptions of more frequent dosing both in sedentary and exercise-trained young mice (3,4,5). Besides glucose homeostasis, rapamycin did not hinder skeletal muscle and physical performance after voluntary exercise in young, female mice (4). However, it remains unknown how different rapamycin dosing schedules impact metabolic, physical and molecular adaptions to voluntary exercise training in the context of aging. Our preliminary findings suggest that 8-weeks of progressive weighted wheel running (PWR) (6) started later in life (22 months old), partially restored age-related deficits in adiposity, glucose metabolism, physical performance, skeletal muscle mass, and a composite skeletal muscle multi--omic aging score toward that of young, sedentary controls (5 months old). However, frequent rapamycin (2mg/kg, 5d/wk) exacerbated age- related pro-inflammatory pathways and induced whole-body insulin resistance in sedentary conditions and appears to attenuate or prevent PWR-induced improvements to insulin sensitivity, treadmill exercise capacity, skeletal muscle mass, and skeletal muscle multi-omic aging score. Intermittent rapamycin (2mg/kg, 1d/wk) alleviated many of the detrimental effects of more frequent dosing in both sedentary and PWR trained mice. We also identified that the extent by which PWR, with or without rapamycin, modified the skeletal muscle multi-omic aging score correlated with changes to cardiometabolic fitness. Collectively, these data indicate that intermittent dosing strategies may alleviate many of the inhibitory effects of more frequent rapamycin dosing schedules on systemic, skeletal muscle, and molecular adaptations to voluntary exercise in older mice. However, neither rapamycin dosing schedule potentiated the health benefits of exercise in the context of aging.

Keywords: *aging, metabolism, muscle hypertrophy, mTOR, insulin resistance.*