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A Unique Drug Cocktail Slows Aging in Mice

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Abstract

The process of aging as a physical process is due to a decrease of function in multiple interconnected biological pathways. It thus follows that in order to increase resilience to aging, several pathways must be targeted. Acarbose, as comparative enzyme was proven to delay glucose absorption and lower postprandial hyperglycemia, as well as increase lifespan in HET3 mice in previous NIA intervention testing programs. Rapamycin inhibits mTOR1 function through binding with its immunophilin which is regulated by upstream pathways responsive to nutrient intake therefore suppress autophagy impairment. PBA is a broad-spectrum inhibitor and an active ER stress chaperone that inhibits histone deacetylation and decreases ER stress. This study was designed to determine whether the effects of a drug combination would create an increase in resilience to aging through relative senescence quantification. The drug cocktail was given to a cohort of mice via oral delivery in their feed starting at age 21 months and ending at the age of 24 months when many of the chronic and histological lesions associated with aging are quite apparent. Another group of mice of the same number were fed regular feed for control comparison. P53 and P16 are the two most common senescence pathways and were examined for the purpose of this study though 2 step RT-qPCR on their respective primers. Preliminary data from liver samples showed that cocktail treated mice had less P16 expression than control mice but similar levels of P21. Senescence expression will be evaluated and relatively quantified on major organs to further investigate the cellular mechanism of testing the drug cocktail. These observations are important as these drugs are prescribed commonly for humans, and their potential in increasing resistance to aging in mice. could provide a method for increasing resilience to aging in humans as well as developing poly-pharmaceutical therapies against age related diseases.

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Introduction

Aging is the result of gradual failure of multiple pathways and single drugs are unable to target all of them. Therefore, a cocktail was designed of three drugs known for their impact on separate aging pathways. The expectation was that these three drugs would act in compliment to each other and have great effects on preventing the failure of these pathways. This concept was tested in aging mice fed a diet medicated with the cocktail for 3 months and tested for performance, fat mass, and senescence.

Objective

Our objective is to determine if there is a reduction in physical phenotypic and biochemical senescent markers when a drug cocktail containing Rapamycin, Acarbose, and Phenylbutyrate is administered in aging mice.

Methods

C57BL/6 female mice, 21 months of age, were used in the study. 4 cohorts of mice (SLAM 1 – 4) each containing 8 mice were divided in half. One half received the cocktail in their food while the other received food without the cocktail. Food intake was monitored weekly to ensure consistent access to the drug. Percent body fat mass was measured weekly using quantitative magnetic resonance imaging. At the end of 3 months, the mice were tested in a box maze, designed to test learning capabilities (Figure 1), rotarod, designed to test physical endurance, and a grip strength test, designed to measure muscle strength. Assays were then performed on the mouse tissues to determine levels of biochemical senescence markers through quantitative polymerase chain reaction.

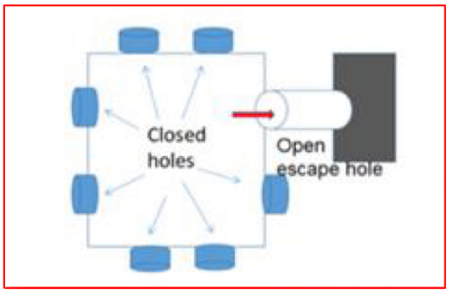

Figure 1: Box maze learning paradigm with four 2-minute trials

Results and Discussion

Mice fed the cocktail demonstrated lesser effects of learning impairment than mice who did not receive the cocktail as seen in Figure 2, $p \leq 0.05$. They also demonstrated longer run times on the rotarod (Figure 3) and demonstrated higher force per body weight values in the grip strength test (Figure 4), $p \leq 0.05$ for both graphs. Lastly, mice fed the cocktail demonstrated lower body fat percent over the three-month period when compared to mice who did not receive the cocktail (Figure 5) $p \leq 0.05$. P16, a senescence marker, was found in significantly lower levels in cocktail mouse liver samples as opposed to mice who did not receive the cocktail (Figure 6), $p \leq 0.05$. Overall, aging mice fed the cocktail diet did better in physical performance tests, were leaner, and had less senescence than mice fed the control diet. These very preliminary observations suggest the cocktail robustly slowed aging in mice by targeting multiple aging processes. The three drugs are individually used for clinical purposes other than aging. Since they are safe, inexpensive, and readily available, the cocktail represents a prototype for considering clinical trials to slow aging in older people.

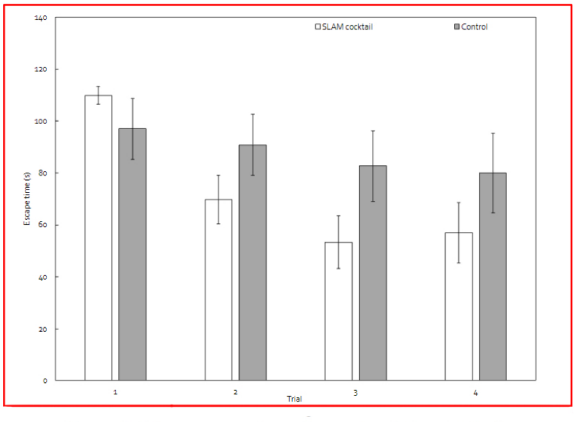

Figure 2: The average times for each of four trials for mice fed the cocktail and mice not fed the cocktail.

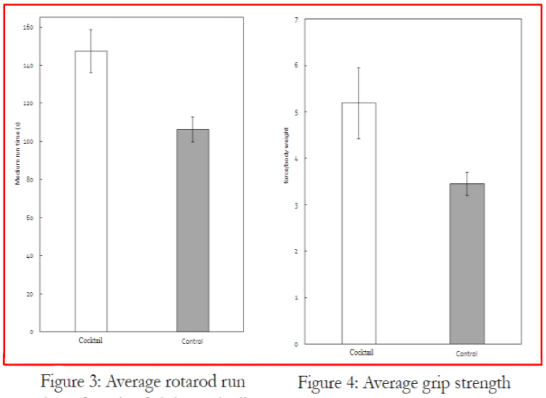

Figure 3: Average rotarod run times for mice fed the cocktail and mice not fed the cocktail.

Figure 4: Average grip strength values for mice fed the cocktail and mice not fed the cocktail.

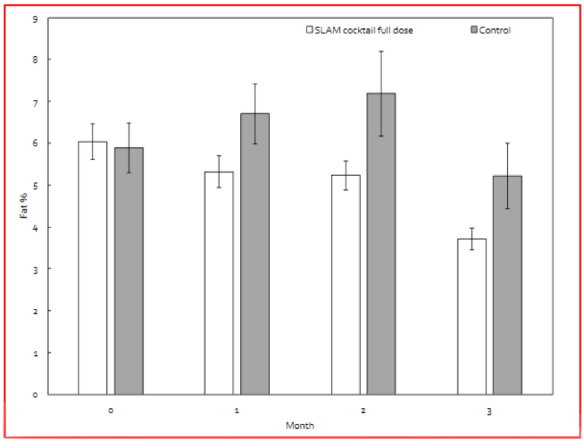

Figure 5: Average percent body fat taken monthly for mice fed the cocktail and mice not fed the cocktail.

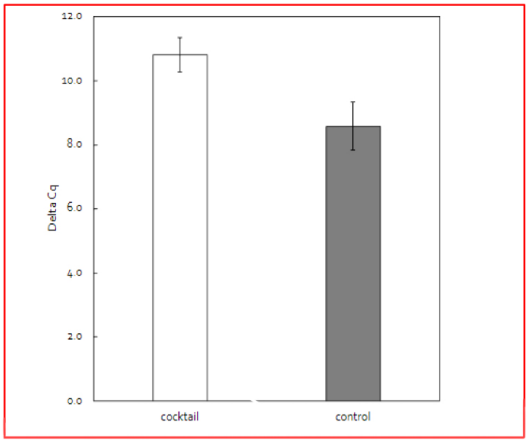

Figure 6: Average levels of P16 in mice fed the cocktail and mice not fed the cocktail.

Acknowledgements

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