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To assess the differential effects of exercise with age, Young (Y, 10-12 weeks) and Old (O, 23-25 months) mice were subjected to regimented treadmill running or no regimented exercise. Y, trained mice experienced a significant increase in maximal distance running, maximal speed of running, and lean muscle mass in comparison to age-matched, untrained controls. O mice did not improve significantly in any of these measures following training. Transcriptome analysis of gastrocnemius from Y mice demonstrated differential regulation of 120 genes with exercise. None of these genes were similarly regulated in the O group. Genes most upregulated following exercise in Y mice were direct targets of the hypoxia signaling pathway. Immunoblotting demonstrated that aryl hydrocarbon receptor nuclear translocator (ARNT), a critical regulator of hypoxia signaling, increased 3-fold with exercise in Y mice, but this increase was absent in O mice following exercise. To assess whether this loss of ARNT in O muscle impaired the exercise response, we generated a mouse with inducible, skeletal muscle-specific knockout of ARNT (ARNT muscle (m) KO). Following regimented exercise, ARNT mKO mice did not improve maximal distance running, maximal running speed, or lean muscle mass in comparison to untrained ARNT mKO mice. Littermate, age-matched ARNT wild type mice increased significantly in all of these measures following training. Administration of ML228, an ARNT agonist, increased maximal running distance and speed in response to exercise training in O mice. These results suggest that restoration of ARNT and hypoxia signaling may restore the physiologic response to exercise in aging.

MECHANISMS OF CELL NON-AUTONOMOUS LONGEVITY REGULATION

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An organism's ability to respond to stress is crucial for long-term survival. These stress responses are coordinated by distinct but overlapping pathways, many of which also regulate longevity across taxa. Our previous work identified a cell non-autonomous signaling pathway led by the hypoxia-inducible factor and resulting in induction of flavin-containing monooxygenase-2 (fmo-2) to promote health and longevity. Our current work identifies a distinct cell non-autonomous pathway downstream of dietary restriction (DR) that also relies on fmo-2 induction to promote health and longevity. We now find that these cell non-autonomous pathways can be mimicked by small molecule interventions that increase longevity by inducing fmo-2. Based on the commonalities of these pathways, we hypothesized that fmo-2, a classically annotated xenobiotic enzyme, might play a key endogenous role in responding to metabolic stress. Our resulting data, using metabolic profiling and further epistatic analysis, both support this hypothesis and link fmo-2's mechanism to modifications in one-carbon metabolism (OCM), a key intermediate pathway consisting of the folate and methionine cycles. Using mathematical modeling and a labeled metabolomics approach, we were able to further identify the likely mechanism of fmo-2-mediated metabolic effects and connect them to both OCM and downstream components. We propose that fmo-2 is induced cell non-autonomously to modify systemic metabolism and longevity, and that fmo-2 is a key member of a conserved metabolic stress response.

MODERATE CALORIE RESTRICTION ENHANCES HEPATIC GLUCAGON SENSITIVITY IN AGED MICE

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Chronic calorie restriction (CR) without malnutrition delays the onset of aging, extends lifespan, and improves metabolic function in many species. These CR-induced benefits have largely concentrated on the role of insulin signaling, while ignoring its counter-regulatory hormone, glucagon. Like insulin, hyperglucagonemia and decreased glucagon sensitivity are associated with impaired glucose homeostasis and decreased longevity. Conversely, activation of target molecules downstream of glucagon signaling such as AMPK and FGF21 are known to ameliorate these age-related impairments in metabolic function. To investigate the potential role of glucagon receptor signaling in CR-induced improvements in aging, we have implemented a moderate 15% CR in the mouse. Our studies show that a 15% calorie restriction initiated at 4 months of age enhances hypoglycemia-stimulated glucagon secretion ($P<.01$) and decreases basal serum glucagon ($P<.01$), while having no effect on glucagon receptor expression at the liver in 26-month-old mice. Consistent with enhanced hepatic glucagon sensitivity, CR increases glucagon-stimulated hepatic cyclic AMP production ($P<.05$). Glucagon is a primary regulator of AMPK activation and FGF21 release, both of which have been proposed as key molecules to account for CR-induced benefits to aging. CR increases both hepatic AMPK activation ($P<.05$) and FGF21 mRNA expression ($P<.05$). Additionally, CR reduces hepatic lipid accumulation ($P<.05$), and decreases fasting respiratory quotient ($P<.001$), indicating an increase in lipid oxidation. Our studies demonstrate that a moderate (15%) CR regimen enhances glucagon sensitivity and decreases hepatic lipid accumulation in aged mice. Thus, we propose glucagon signaling as a mediator of CR-induced improvements in aging.

REDUCED MUSCLE OXIDATIVE CAPACITY DURING AND AFTER EXERCISE IN OLDER ADULTS WITH OBESITY

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Objective: Obesity and physical activity are two major factors affecting aerobic performance in older adults. The underlying mechanisms of the causes are still unknown. Oxidative capacity, muscles' maximal capacity to utilize oxygen, is a part of aerobic performance. Muscle oxygen level (SmO2), a measure of oxidative capacity, reflects the balance between oxygen delivery and oxygen demand. When