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Heterochronic parabiosis is a powerful rejuvenation model in aging research. Due to limitations in the duration of blood sharing and/or physical attachment, it is currently unclear if parabiosis retards the molecular signatures of aging or affects healthspan/lifespan in the mouse. Here, we describe a long-term heterochronic parabiosis model, which appears to slow down the aging process. We observed a "deceleration" of biological age based on molecular aging biomarkers estimated with DNA methylation clock and RNA-seq signature analysis. The slowing of biological aging was accompanied by systemic amelioration of aging phenotypes. Consistent with these findings, we found that aged mice, which underwent heterochronic parabiosis, had an increased healthspan and lifespan. Overall, our study re-introduces a prolonged parabiosis and detachment model as a novel rejuvenation therapy, suggesting that a systemic reset of biological age in old organisms can be achieved through the exposure to young environment.

DIET AND STRESS IMPAIR OVARIAN FUNCTION IN MID-LIFE, INCREASING RISK OF CHRONIC DISEASES OF AGING IN PRIMATES

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Ovarian dysfunction increases risk for chronic diseases of aging including cardiovascular disease, depression, cognitive impairment, and bone and muscle loss which promote frailty. Psychosocial stress disrupts ovarian function and recent observations suggest that Western diet may also. Determination of causal relationships among diet, psychosocial stress, and ovarian physiology is difficult in humans. Nonhuman primates provide relevant opportunities to investigate diet and psychosocial effects on ovarian physiology and aging because, like humans, they have monthly menstrual cycles and recapitulate many aging-related processes similar to humans. We examined ovarian function in 38 socially housed, middle-aged females fed either a Western or Mediterranean diet for 26 months (~ an 8-year period for humans). During the last 12 months, we examined cycle length, peak progesterone per cycle, and frequency of anovulatory cycles using blood sampling (3/week) and vaginal swabbing (6/week). Repeated measures analysis revealed that like middle-aged women, cycle length increased, and progesterone levels fell over time, suggesting that ovarian dysfunction generally increased in our sample with time. In addition, both Western diet and the stress of low social status reduced progesterone levels, disrupting ovarian function, and increasing risk of chronic diseases of aging. This study demonstrates the additive negative effects of poor diet and psychosocial stress on ovarian physiology in mid-life and lays the groundwork for future investigations to uncover associated metabolic signatures of accelerated aging. The results also suggest that a Mediterranean diet may exert a protective influence against ovarian dysfunction and its pathologic sequelae.

EXERCISE DURING CHILDHOOD PROTECTS AGAINST CARDIAC DYSFUNCTION LATER IN LIFE

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Cardiovascular disease continues to be a major cause of morbidity and mortality, particularly in aging populations. Exercise is amongst the most cardioprotective interventions identified to date, with early in life exercise such as during the juvenile period potentially imparting even more cardioprotective outcomes due to the plasticity of the developing heart. To test the hypothesis that juvenile exercise would impart later in life cardioprotection, we exercised juvenile male and female mice via voluntary wheel running from 3-5 weeks of age and then exposed them to cardiac stress by isoproterenol (ISO) at 4-6 and 18 months of age in adulthood and older age, respectively. We compared cardiac function and remodeling to sedentary control animals, sedentary animals who received ISO, and adult and aged mice that exercised for two weeks immediately before ISO exposure. Juvenile mice engaged in voluntarily wheel running, with male mice running 1.3 ± 0.8 km and female mice 2.8 ± 1.0 km a day. Echocardiography suggested that these juvenile animals underwent running-induced cardiac remodeling as evidenced by higher ejection fraction and stroke volume compared to sedentary controls. Exercise in the juvenile period attenuated ISO-induced cardiac hypertrophy and remodeling later in life compared to sedentary animals and those that exercised immediately before ISO administration. The mechanisms by which early versus late exercise is protective in adult and aged mice are under investigation. Further ongoing work will identify the adaptations induced by exercise in the juvenile heart that may help improve cardiac aging.

EXERCISE-INDUCED TRANSCRIPTIONAL CHANGES IN AGED SKELETAL MUSCLE

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Exercise is beneficial for physical functions across all ages. However, the response to exercise shifts from anabolism, resulting in limited gain of muscle strength and endurance. These changes likely reflect age-related alterations in transcriptional response underlying the muscular adaptation to exercise. The exact changes in gene expression accompanying exercise, however, are largely unknown, and elucidating them is of a great clinical interest for optimizing the exercise-based therapies for sarcopenia. In order to characterize the exercise-induced transcriptomic changes in aged muscle, a paired-end RNA sequencing was performed on the rRNA-depleted total RNA extracted from the gastrocnemius muscles of 24 months-old mice after 8 weeks of regimented exercise (exercise group) or sedentary activities (sedentary group). Differential gene expression analysis revealed