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Review

Basic concepts about genes, inactivity and aging

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Remarkably, 80-year-old humans who have partaken in lifelong aerobic or strength training have maximal aerobic capacities or muscle strengths comparable with that of sedentary individuals aged 50 or 55-year-old, respectively. Such delays in functional aging are clinically significant because lower aerobic and lower strength capacities increase the risk of premature death. In this short review, we speculate that the lack of daily physical activity induces evolutionarily selected mechanisms to use or lose, one of which is related to nutritional status.

Aging and frailty – a programmed genetic process modifiable by exercise?

Aging is associated with declines in the ability to perform physical work. Declines in both aerobic-endurance capacity (defined as the work duration to fatigue when oxygen consumption by mitochondria matches ADP and AMP production; aerobic endurance declines with aging due to a loss in maximal aerobic capacity) and muscle strength (due to loss of muscle mass) lead to aerobic and strength frailty, respectively, with advanced age. Gulve et al. (1993) demonstrated that lifelong voluntary physical activity in rats decreases by nearly 2/3 with advanced age. Remarkably, the lack of lifelong physical activity, itself, accelerates the loss of both aerobic and strength capacities by 25–30 years (Fig. 1); therefore, physical inactivity advances the age of onset of physical frailty. The molecular mechanisms underlying the decline in physical work capacity as one ages are not fully understood.

Frailty

Fried et al. (2001) define *frailty* as a distinct clinical syndrome that infers a high level of health risk, particularly, an increased vulnerability to stressors (e.g., infection, injury or even changes in medication), a condition that characterizes many older adults. Phenotypical descriptions from this report focus on the functional manifestations of frailty involving dysregulated energetics, muscle weakness, reduced exercise tolerance, decreased walking speed, physical inactivity and weight loss. In the current review, we generalize the phenotypic descriptions presented by Fried and colleagues with the terms ''aerobic and strength frailties.''

Maximal oxygen consumption (VO_{2max}) declines with aging

The maximal capacity for the body to consume oxygen during physical exertion determines the VO_{2max} (synonymous with peak VO_2, aerobic capacity and cardiorespiratory fitness). During the third decade of life, VO_{2max} begins to decline. However, lifelong physical activity delays the onset of aerobic frailty (defined as $VO_{2max} < 18$ mL/kg/min; Carr et al., 2006). In fact, using the data of Fitzgerald et al. (1997), Tanaka and Seals (2003), we estimate that aerobic-endurance-trained individuals reach aerobic frailty some 30 years later in life, when compared with habitually sedentary individuals. This progressive reduction in VO_{2max} appears to be the primary mechanism associated with declines in aerobic-endurance performance with advanced age (Tanaka & Seals, 2008). Evidence shows that decreases in maximal stroke volume, heart rate and arterio-venous O_2 difference all appear to contribute to the age-related reductions in VO_{2max} in endurance-trained (''Masters'') athletes, despite continued aerobic-endurance training (Tanaka & Seals, 2008). Unfortunately, the molecular basis for these reductions is unknown. Human models of physical inactivity reveal massive losses in VO_{2max} in very short periods of time, relative to the

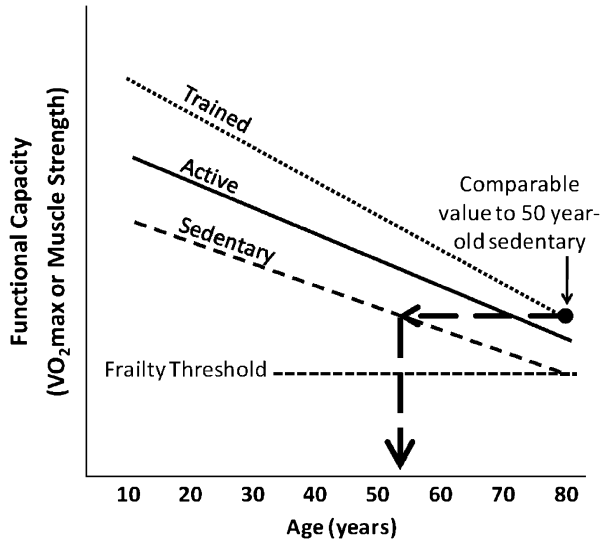

Fig. 1. Schematic depicting that physical activity delays the decline in physical function (VO_{2max} or muscle strength) with aging. Remarkably, a lifelong, physically trained 80-year-old has comparable values for VO_{2max} and muscle strength as a sedentary 50–55-year-old. Figure is modified from Fitzgerald et al. (1997), with contributions from Pearson et al. (2002), with the original slopes maintained. The frailty threshold is defined as $VO_{2max} < 18$ mL/kg/min by Carr et al. (2006).

time span of aging. When young, healthy men, not partaking in any structured exercise programs, reduced their daily step number from 10 000 to 1500/day, VO_{2max} declined 7% in just 14 days (Olsen et al., 2008). Furthermore, VO_{2max} decreased 28% after 20 days of continuous bed rest in young, healthy, sedentary men (McGuire et al., 2001). Remarkably, this decline in VO_{2max} was greater than occurred in these same men from ages of 20 to 60 years upon a 30-year follow-up (11% on average). Thus, we already know how to delay much of the decline in VO_{2max} with aging – just partake in regular aerobic-endurance exercise. However, what we do not know are the genes and mechanisms by which the lack of physical activity accelerates the onset of aerobic frailty with aging.

Skeletal muscle strength declines with aging

Aging is associated with a decrease in skeletal muscle mass, beginning in the third decade of life and accelerating after the fifth decade (Lexell et al., 1986). The decrease is explained largely by a greater decline in the lower body skeletal muscle mass than in the arm mass (Janssen et al., 2000). High-resistance strength training for older people does not slow the rate of decline in muscle function with increasing age, but does result in a shift upward to a new, higher absolute level of muscle mass that has a similar relative rate of decline as control subjects. However, Pearson et al. (2002) demonstrated that the average power generated by 80-year-old resistance-trained, weightlifting-champion athletes was equivalent to that of 55-year-old untrained subjects, indicating that resistance training may delay the onset of physical frailty by some 25 years, not unlike aerobic-endurance training. Again, we do not know the genes and mechanisms by which the lack of resistance (strength) training accelerates the onset on physical frailty with aging.

Loss of VO_{2max} and muscle mass increases the risk of mortality

As described above, aerobic and physical frailties are inherent with the aging process. However, a vicious cycle persists with advanced aging; the loss of aerobic capacity and skeletal muscle mass causes declines in physical activity and strength, which consequentially lead to further reductions in aerobic capacity and skeletal muscle mass. The clinical significance of the loss of aerobic capacity and/or skeletal muscle mass is that mortality risk increases as aerobic capacity and skeletal mass decrease (Metter et al., 2002).

Summary

Habitual, lifelong physical activity delays the loss of VO_{2max} and skeletal muscle mass with aging, but does not prevent their eventual decline to reach the threshold of aerobic and strength frailties. Impressively, the delay has a remarkable clinical significance. At 80 years of age, individuals maintaining aerobic-endurance training throughout their lifespan have a VO_{2max} of the average 50-year-old individual who never exercises, and 80-year-old individuals engaging in strength training throughout their lives have the strength of the average 55-year-old individual who never exercises. Thus, new pharmacological therapies are not needed to delay frailty in those individuals without physical constraints as a powerful one (aerobic and strength exercise) already exist.

High capacity for physical activity – a naturally selected phenotype?

Why was the body designed for physical activity to maintain VO_{2max} and muscle mass?

Although there are many speculative answers to the question posed above, we favor one notion by Bennett and Rubin (1979) – "The selective advantages of increased activity capacity are not subtle but rather are central to survival and reproduction. An animal with greater stamina has an advantage that is readily comprehensible in selective terms ... It can sustain greater levels of pursuit or flight in gathering food or avoiding becoming food ... It will be superior in territorial defense or invasion ... It will be

more successful in courtship and mating.'' Extending the above, we favor the notion that those with lower capacities for aerobic and strength physical activities were more likely to have their gene pools extinguished before reaching reproductive age, thus suggesting the possibility of a high physically active phenotype produced in the natural selection process.

Experimental selection can separate low-capacity runners from high-capacity runners

Mice selectively bred for the longest distances obtained by voluntary running in wheels had 10–20% higher VO_{2max} than the selected lowest distance runners did (Rezende et al., 2006). In a second example, rats were selectively bred for intrinsic (i.e., untrained) capacity to run the furthest distance before they contacted an electric shock for the third time during aerobic treadmill running. After 11 generations of selection, high-capacity runners had a 347% longer running distance compared with the low-capacity runners (Wisloff et al., 2005) and 50% higher VO_{2max} (Gonzalez et al., 2006). Furthermore, Bronikowski et al. (2006) demonstrated that the behavioral effects of exercise, when selected for high wheel running capacity at an early age, declines throughout the lifespan, suggesting a decrease in genetic heterogeneity for the genes involved in increased exercise capacity over age.

Loss of functional capacity with physical inactivity – a conserved survival mechanism?

What survival advantage could be gained by the loss of skeletal muscle?

We make the conjecture that skeletal muscle atrophy from lack of usage against a load is related to a survival mechanism selected to conserve or substitute for low stores of glycogen in the body. We have the notion that portions of the signaling pathway initiated by an insufficient supply of amino acids to skeletal muscle (from a lack of food) are shared by the lack of muscle contraction against a load.

Skeletal muscle atrophies 20–50% in immobilized (Booth, 1982) and hind limb-suspended (Thomason & Booth, 1990) limbs of rats. It is our notion that atrophy-signaling pathways were selected by insufficient nutrition (supply of amino acids) and that the nutrition pathway intertwined with the inactivity atrophy pathway. Our notion was initiated by data from Biolo et al. (1995), whereby in fasting humans, skeletal muscle protein balance is negative (i.e., there is a net release of amino acids from skeletal muscle), implying that protein degradation exceeds protein synthesis in the skeletal muscle. Applying resistance (strength) exercise in a fasted state attenuates the negative protein balance. Resistance exercise in the fasting state increases both protein synthesis and degradation, but net protein balance remains negative. However, either infusing or ingesting amino acids produces a positive net protein balance across the human skeletal muscle in both the resting muscle and the resistant-exercised muscle, with the positive net balance being augmented in the exercised muscle, compared with the resting muscle. It is our conjecture that the amino acid regulation of protein balance in resistance exercise is generated by the function of providing amino acids from skeletal muscle to the liver for gluconeogenesis during an overnight fast. Our bodies have a finite capacity to store glycosal units for fuel, as the maximal glycogen storage in a sedentary human is ~ 900 kcal. Thousands of years ago, our ancestors' bodies must have gone through daily cycles of skeletal muscle protein degradation and liver gluconeogenesis to conserve glycogen stores for those durations lasting over one day without food ingestion (our ancestors did not have guaranteed 24-h access to food as many do today). Based on this, we make the conjecture that mechanisms regulating inactivity-induced skeletal muscle atrophy are conserved from a survival mechanism that existed when our ancestors did not have on-demand access to food.

Perspectives

Basic concepts and logical speculations underlie the decline in physical work capacity with aging. Exercise can delay frailty for three decades; however, frailty with advanced age is inevitable. While pharmaceutical drugs might be needed to treat conditions associated with frailty in disabled and elderly individuals, the benefits of daily exercise extend to so many organs and body systems that a single pharmaceutical chemical to counter frailty will be unlikely to counter both aerobic and strength frailties. Furthermore, a single pharmaceutical chemical can never counter the functional decline in all organ systems with aging. Exercise has vast beneficial effects on a multitude of organs and body systems and delays aging-associated losses in cognitive function, osteoporosis, insulin resistance, atherosclerosis, certain site-specific cancers, depression and immunity, but does not delay the loss of maximal heart rate. Scientists and pharmaceutical companies lacking appropriate knowledge of the pleiotropic effects of exercise need to understand that it is unethical to label any one drug as an ''exercise pill.''

Key words: maximal oxygen uptake, Sarcopenia, exercise, mortality, natural selection.

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