And if we manage to lengthen life - even if that's not the case today - there are so many men and women to love and so many books to read, that three centuries isn't very long at all. Luc Ferry Philosopher. Interview on Europe 1, April 2016.

This month's theme: Muscular System and Longevity

The aging of the muscular system in humans, also known as sarcopenia, involves a complex interplay of physiological changes that lead to the gradual loss of muscle mass, strength, and function.

Individual muscle fibers, especially type II (fast-twitch) fibers, shrink and reduce in number with age. Type II fibers are responsible for quick and powerful movements, so their loss contributes to decreased strength and speed. Overall muscle mass declines with age due to the loss of muscle fibers and the reduction in the size of remaining fibers. This process is influenced by hormonal changes, decreased physical activity, and altered protein metabolism. The neuromuscular junction (NMJ), where nerve cells connect with muscle fibers, also deteriorates with age. This degeneration leads to impaired communication between the nervous system and muscles, resulting in reduced muscle function and strength. We also see mitochondrial dysfunction, the energy-producing organelles in cells, become less efficient with age. This dysfunction leads to reduced energy availability for muscle contraction and increased production of reactive oxygen species (ROS), which can damage cellular components.

Aging affects the balance between muscle protein synthesis and degradation. Levels of anabolic hormones such as growth hormone, testosterone, and insulin-like growth factor 1 (IGF-1) decrease with age. These hormones play crucial roles in muscle maintenance and repair. Chronic low-grade inflammation, often referred to as "inflammaging," is associated with aging. Pro-inflammatory cytokines can promote muscle catabolism and interfere with muscle repair and regeneration processes. Satellite cells are muscle stem cells that play a key role in muscle repair and regeneration. Their number and function also decline with age, impairing the muscle's ability to recover from injury and maintain muscle mass.

Aging is often accompanied by a decrease in physical activity levels, which accelerates muscle loss. Regular exercise, particularly resistance training, can mitigate some of the effects of aging on the muscular system by promoting muscle protein synthesis and improving neuromuscular function.

Sarcopenia

It is defined as the age-related, involuntary loss of skeletal muscle mass and strength. Starting as early as the 4th decade of life, evidence suggests that both skeletal muscle mass and strength decline in a linear fashion, with up to 50% of muscle mass being lost by the 8th decade of life. Since muscle mass accounts for up to 60% of body mass, pathological changes to this metabolically active tissue can have significant consequences for older adults. The strength and functional declines associated with sarcopenia can lead to severe outcomes, including loss of function, disability, and frailty. Additionally, sarcopenia is linked to both acute and chronic disease states, increased insulin resistance, fatigue, falls, and ultimately mortality. Among chronic diseases, sarcopenia is particularly associated with rheumatologic conditions, especially rheumatoid arthritis (RA) in women.

Overall declines in the size and number of skeletal muscle fibers characterize the physiological and morphological changes in skeletal muscle with advancing age. Additionally, there is a significant infiltration of fibrous and adipose tissue into the skeletal muscle. Satellite cells, which are skeletal muscle precursor cells residing in a quiescent state associated with myofibrils, also undergo important age-related changes. These satellite cells are activated to initiate skeletal muscle repair and regeneration in response to the stress of heavy muscle use, such as weight-bearing activities, or traumatic events, such as injury.

Molecular Mechanisms of Muscle Aging

In older individuals, the balance between protein synthesis and breakdown may be disrupted, leading to increased muscle catabolism and a reduction in skeletal muscle mass. These changes are characteristic of old age and frailty. Frailty has been reported to exacerbate aging-related disruptions in protein metabolism. A lack of dietary protein is a potential factor contributing to decreased muscle protein synthesis in the elderly. The dietary protein intake of old people is often below the recommended daily allowance for both men and women.

Gender Differences in Muscle Aging

Higher rates of muscle mass loss during aging have been reported in males compared to females and a higher prevalence of sarcopenia has been observed in males compared to females. Some studies have identified sex-specific markers for sarcopenia. One electron microscopy study measured mitochondrial content and found that intermyofibrillar mitochondrial size primarily decreased in older females, not in older males. Moreover, in the FITAAL study, it was found that intramuscular (acetyl) carnitine levels decreased with age in females but not in males. These findings suggest that during aging, females experience more changes in mitochondrial content and function compared to males. Additionally, the composition of the plasma proteome is known to change with aging, and interestingly, a large human study found that these age-associated changes were highly sex-specific.

Therapies

A study investigated the long-term effects of muscle hypertrophy, achieved through the overexpression of human follistatin (a myostatin antagonist), on neuromuscular integrity in C57BL/6J mice aged 24 to 27 months. Follistatin was delivered via self-complementary

adeno-associated virus, resulting in significant improvements in muscle weight and torque production. The treatment enhanced neuromuscular junction innervation and transmission, although it did not affect age-related motor unit losses. These findings show that follistatin-induced muscle hypertrophy not only boosts muscle weight and torque but also mitigates age-related neuromuscular junction degeneration in mice.

The team of George Church along with Liz Parish from Bioviva Science demonstrated that using CMV as a gene therapy vector allows for monthly inhaled or intraperitoneal treatment for aging-related decline. In a murine model, exogenous telomerase reverse transcriptase (TERT) or follistatin (FST) genes were delivered safely and effectively. This treatment significantly improved aging biomarkers and increased mouse lifespan by up to 41% without raising cancer risk, offering a promising approach to address the global rise in aging-related diseases. As seen in other studies, FST-treated mice showed increased body mass, correlating with muscle mass gains. FST enhances mitochondrial biogenesis, energy metabolism, cellular respiration, and thermogenesis, promoting the browning of white adipose tissue. This regimen required monthly administration to maintain continuous effects, which could be beneficial for episodic treatment needs, reducing long-term adverse reaction risks.

The good news of the month: Government-funded research aims to Replace Aging Brain with Lab-Grown Tissue

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Jean Hébert (A genetics and neuroscience professor at the Albert Einstein School of Medicine in The Bronx), recently hired by the US Advanced Projects Agency for Health (ARPA-H), spearheads a groundbreaking anti-aging approach by replacing parts of the human brain with cloned tissues. His research focuses on progressively replacing brain parts with young, lab-grown tissues, allowing the brain to adapt and maintain its functions.

This could preserve memories and key identity facets, leading to significant advancements in anti-aging treatments. His innovative work, if successful, could lead to breakthroughs in reversing brain aging and enhancing human longevity.

For more information

- Heales, Longevity Escape Velocity Foundation, International Longevity Alliance, Longecity, and Lifespan.io
- Heales Monthly Science News
- Heales YouTube channel
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