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Sarcopenia and protein metabolism and its intervention mechanism

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Abstract: *Slowing the development of skeletal muscle senescence is the key to achieving "active aging" policies. We analyzed the symptoms and causative mechanisms of Sarcopenia by using literature and logical analysis methods, and hypothesized that the imbalance of protein metabolism caused by a series of physiological and lifestyle changes in the elderly population accompanied by aging is the direct cause of aging, and then elucidated the potentially effective interventional mechanisms of Sarcopenia from the perspective of the interventions of nutrition and exercise on protein metabolism. The results suggest that exercise and nutritional interventions have positive effects in the study of interventions to promote protein synthesis and inhibit degradation; however, whether the combined interventions can complement each other and synergistically promote the improvement of Sarcopenia remains controversial, and the mechanisms need to be further explored.*

Keywords: *Aging, Sarcopenia, Protein metabolic, Mechanisms of exercise nutrition intervention*

1. Introduction

According to statistics[1], by the end of 2022, there were 28.04 million people aged 60 years and above in China, accounting for 19.8% of the total population. Among them, there were 20.978 million people aged 65 and above, accounting for 14.9% of the total population. China is already considered a major country with an aging society. In the aging process of the human body, there has always been a saying that "the legs age first". Therefore, slowing down the development of skeletal muscle aging is not only a necessary part of achieving the strategic layout of "healthy aging", but also the key to realizing the policies of "active aging".

2. The characteristics and causes of Sarcopenia

2.1 The main features of Sarcopenia

Sarcopenia[2], is a syndrome that is essentially characterized by progressive, circumscribed loss of skeletal muscle mass and strength, with serious consequences such as limitation of the body's mobility, reduction in the quality of life, and even an increased risk of death. The clinical diagnostic criteria are a decrease in skeletal muscle mass and a decrease in its function (including a decrease in skeletal muscle strength and/or a decrease in physical activity). According to the EWGSOP, the diagnosis requires two features: a decrease in the mass of the skeletal muscle, and a decrease in its function, which must be present, and the diagnosis is not directly confirmed by the absence of one of these features.

That is what distinguishes it from simple amyotrophic and pathological amyotrophia. It has laid the foundation for the feasibility of subsequent nutrition and exercise interventions and is naturally a current research hotspot in areas related to geriatric diseases.

2.2 The cause and mechanism of Sarcopenia

The many factors affecting the development of Sarcopenia can be summarized in two main areas: first, the changes in the body with age. Changes in neurological, hormonal, metabolic, and immune functions at the macroscopic level of the body, as well as shifts in the skeletal muscle's gene expression profile, fiber type and number, neuromuscular coupling, and protein metabolism, etc., will show varying levels and degrees of growth or loss of both muscle mass and muscle strength[3]. Secondly, lifestyle changes[4], particularly alterations in the physiological system of the elderly, are largely dependent on adjusting the level of physical activity. When physical strength declines, activity

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decreases, leading to a decline in function. The reduction in exercise exacerbates a series of vicious circles, resulting in a negative impact on health. The quality of life of the elderly and the decline in the metabolic efficiency of the organism itself result in a lower level of nutritional intake. Morley JE et al.[5] reported that 32%-41% of females and 22%-38% of males in the elderly population aged >50 years, respectively, consumed less than the recommended (0.8 g/kg) level of protein per day. It has also been observed that aging skeletal muscle is not very sensitive to the stimulation of lower concentrations of amino acids, i.e., it shows signs of "protein synthesis resistance" in the elderly[3].

The intrinsic mechanism of Sarcopenia is closely related to skeletal muscle cell apoptosis, imbalance of protein metabolism, oxidative stress, decline and dysfunction of mitochondria, and alteration in the number of microsatellite cells[6-8]. However, the fundamental mechanisms underlying the development of skeletal muscle aging have never been best answered either[9]. Notably, the occurrence of skeletal muscle atrophy is fundamentally linked to the fact that the rate of protein synthesis is lower than the rate of catabolism. Most scholars support the idea that aging-induced skeletal muscle atrophy is mainly due to a reduction in the synthesis of skeletal muscle proteins. However, some studies suggest that the development of aging skeletal muscle atrophy is a result of the dual effects of decreased protein anabolism and increased catabolism.

3. Aging and protein metabolism

3.1 Synthesis and decomposition of proteins

Under normal physiological conditions, protein synthesis and catabolism in the body always maintain a state of dynamic equilibrium to maintain a constant body weight and muscle mass, Scholars at home and abroad agree that the direct cause of the occurrence and development of skeletal muscle atrophy in the elderly is the slowing down of the rate of skeletal muscle protein synthesis and/or the absolute or relative acceleration of the rate of degradation.

3.1.1 Protein anabolism and mTOR

Protein biosynthesis, also known as"Translation", is the second stage of gene expression, and the process can be divided into two major steps. The first step is the activation of amino acids, i.e., the combination of amino acids with specific tRNAs to form aminoacyl-tRNAs, which is carried out in the cytoplasm and is participated in by the enzyme aminoacyl-tRNA synthetase (aaRS, or aminoacyl-acyl-activating enzyme). The enzyme has a high degree of specificity and requires two molecules of ATP to supply energy to activate each amino acid. The second step is the synthesis of the polypeptide chain, which first requires binding to the ribosome and the formation of the translation initiation complex. It consists of three steps: initiation (also translation initiation), elongation, and termination and release, each of which requires the participation of the corresponding protein factors, i.e., the IF, EF, and RF families, and consumes a certain amount of energy.

At present, there are few studies on the intervention of protein synthesis in skeletal muscle from the perspective of regulating amino acid-activating enzymes. It has been reported[10] that leucyl-tRNA synthetase, in addition to its classical function of catalyzing leucyl-tRNA synthesis, directly involved in the decoding of genetic information, and pro-protein synthesis, also has a non-classical function - to participate in the regulation of the TORC1 pathway by sensing the intracellular leucine concentration.

The regulation of translation initiation is the key to eukaryotic gene translation, and its regulation mechanism is the process of phosphorylation. A large number of studies have elucidated the importance of the mammalian target of rapamycin (mTOR) and its signaling pathway involved in the regulation of protein translation. In mammalian cells, there are two different forms of mTOR complexes, including mTORC1(mTOR complex1) and mTORC2(mTOR complex2), of which the central one is mTORC1, whose main role is to phosphorylate the ribosomal S6 protein kinase (p70S6K) and eukaryotic initiation factor 4E binding protein (4EBP1)[11,12], which are the downstream effectors of mTORC1 and play irreplaceable roles in the normalization of protein translation initiation, ribosome generation and peptide chain extension[13]. it was found that the activation process of mTOR and its downstream factors, p70S6K, and 4EBP1, could be blocked by exogenous rapamycin, and also virtually blocked the progression of muscle toward hypertrophy[14], illustrating the great significance of mTOR and its downstream factors, p70S6K and 4EBP1, in promoting muscle hypertrophy.

3.1.2 Multiple pathways of protein catabolism

The main proteolytic pathways in vivo are the ubiquitin-protease pathway, lysosomal pathway,

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cytosolic protease hydrolysis pathway, and mitochondrial protease pathway.

The ubiquitin-proteasome pathway (UPP) is efficient, highly selective, and ATP-dependent. Its main targets are abnormal proteins and endoplasmic reticulum proteins in the body, and it is widely involved in a variety of metabolism. Accelerated degradation of myofibrillar proteins and intracellular denatured and abnormal proteins under fasting versus disease state and stress conditions, respectively, as regulated by the ubiquitin protease pathway. This pathway is responsible for 80-90% of intracellular protein turnover, with further degradation of unfolded proteins in the cytoplasm and myofilaments dissociated by the calpain (calpain, caspase) pathway, including actin and myosin[15]. Current studies have shown that the process of UPP activation is the main mechanism by which degradation of proteins occurs in pathologic states[16]. Its components muscle ring finger 1 (MuRF1) and muscle atrophy F-box (MAFbx, atrogin-1) are both markers of skeletal muscle atrophy, and it has been suggested that the process of ubiquitination is not possible without the participation of these two genes[17], and the up-regulation of the expression of MuRF1 and atrogin-1 with the onset of muscle atrophy also increases the activity of this pathway.

The main targets of the lysosomal pathway are extracellular proteins, plasma proteins, hormones, bacteria, etc., whose degradation is accomplished in lysosomes through the action of phagocytosis; intracellular proteins are phagocytosed by autophagic vesicles to accomplish degradation. This pathway is non-specific and is not primarily relied upon for normal cytosolic protein transport processes under normal conditions. The cytosolic protease hydrolysis pathway consists mainly of the calpain and non-calpain pathway. The breakdown of myofibrils into myofilaments dominated by calpain is the 1st step in myofibrillar protein degradation and is the rate-limiting step for complete protein degradation[18]. Yet there have been few explorations specifically addressing calpain in muscle protein degradation, especially in vivo. In vitro studies have found that full-length skeletal muscle-specific calpain(Calpain-3)is activated by degradation and then participates in actin degradation under the regulation of Ca+ concentration and the enzyme's binding site to myosin; other members of the calpain family are also involved in the degradation of myofilaments into small fragments[18].

3.2 Effects of aging on protein metabolism

Hypotheses and theories about aging can be grouped into two main categories: genetically programmed aging theories and damage accumulation aging theories. Within the theory of genetically programmed aging, the error catastrophe theory is based on the idea that errors of synthesis occurring in DNA or other template molecules are fundamentally due to errors in protein synthesis[19], which is largely supported by recent studies on leucyl tRNA synthetase[10].“Free radical theory” is now a well-recognized doctrine of aging that has both the characteristics of the first type of theory and the connotations of the second type[20].In recent years, the oxidative stress doctrine has been derived from the free radical theory. It has been found that there is some kind of functional relationship between oxidative damage to proteins and reduced grip strength in the elderly. It can be hypothesized that oxidative stress affects protein metabolism in the elderly and is an important cause of the development of Sarcopenia. changes such as reduced total mitochondrial volume increased oxidative damage, and diminished oxidative capacity that occur in aging populations, along with the aging inflammatory response all induce imbalances in protein metabolism[21], which can lead to a reduction in aging skeletal muscle.

At the same time, physiological decline in the elderly, "geriatric anorexia" due to weakened sense of taste, changes in dentition, social isolation, depression, etc., the increase in visceral consumption with age, as well as the decline in digestive and absorptive functions of the elderly[22], lead to the incomplete nutritional intake of the elderly, and thus insufficient replenishment of essential amino acids, which weakened the stimulatory effect on muscle protein synthesis. Some studies have done muscle protein testing in older and younger adults, and comparisons have shown that muscle protein synthesis in older adults exhibits a localized decrease of 20-30%, yet protein degradation is elevated by as much as half[23]; however, other studies have shown that the rate of protein degradation in older adults does not differ from that of younger adults.

4. The intervention mechanism of nutrition and exercise on protein metabolism

4.1 Effects of nutrition and exercise on protein anabolism

Much of the research on the mechanisms of exercise and nutrition interventions has been devoted to

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exploring the direct or indirect regulation of mTOR and its signal transduction pathway. Indirectly, the expression of serine/threonine kinase protein kinase B (PKB, Akt), also known as the PI3K/Akt signaling pathway, is regulated through insulin (INS-1) or insulin-like growth factor (IGF-1), midway through phosphatidylinositol 3 kinase (PI3K)[24]. Exercise promotes elevated levels of IGF-1 in local tissues, which further activates the PI3K/Akt pathway and increases muscle protein synthesis[25], thereby stimulating the proliferation and hypertrophy of muscle tissue. Daoyuan He et al.[26]tested the effect of acute platform running exercise on mTOR protein expression in rat skeletal muscle, and the results showed that IGF-1, PKB, and mTOR were significantly increased, suggesting that acute exercise activated the mTOR signaling pathway, and IGF-1 might be involved in this process; however, the specific mechanism of the changes in the expression of IGF-1 induced by exercise is not yet clear.

Indirect regulation of muscle protein synthesis by nutritional supplementation also occurs primarily through activation of the IGF-1/PI3K/Akt pathway. After 4 weeks of supplementation with branched-chain amino acids to rats with simulated weight loss, it was found that the wet weight of flounder muscle increased by about 41%, and the wet weight-to-body mass ratio went up by about 30%, while serum IGF-1 and testosterone (TESTO) levels all tended to increase[27], suggesting that branched-chain amino acids may promote muscle protein synthesis by stimulating hormone secretion. Fewer reports on nutrition or exercise do not depend on the IGF-1/insulin pathway but act directly on mTOR and its downstream molecules, or the regulation of protein synthesis via TSC1-TSC2, G β L-raptor, and Rheb, especially in somatically aging skeletal muscle.

4.2 Effects of nutrition and exercise on protein catabolism

Because Sarcopenia occurs with more complex mechanisms regulating protein degradation and fewer studies on the mechanisms of exercise and nutritional intervention, a complete and consistent view has not yet been developed. The ubiquitin-proteasome pathway has attracted much attention in the research of intervention mechanisms. The ubiquitin ligases Murf1 and MAFbx, are thought to be substances that mark the degradation of skeletal muscle proteins[28]. FOXO transcription factors are inactivated after phosphorylation by Akt, which in turn blocks the active expression of MURF1 and MAFBX[29].

Skeletal muscle MAFbx and MuRF1 gene expression increased exponentially after a single bout of strenuous exercise[30], which may be regulated by NF-κB signaling and associated with exercise-generated oxidative stress. Myostatin (MSTN), also known as Growth differentiation factor 8, negatively regulates the growth of skeletal muscle and increases its expression with age[31], and its down-regulation is favored by both weight-bearing running and peptide supplementation. However, there are few reports on its regulatory relationship with protein degradation signaling pathways.

Calpain regulates myofibrillar protein degradation, which is the rate-limiting step of skeletal muscle protein degradation. Calcium concentration and calcium Protease inhibitors in cells are involved in regulating the activity of calpain. After activation of calpain by Ca^{2+}, the enzyme quickly binds to surrounding calpain inhibitors, and its activity is inhibited, ensuring that calpain only hydrolyzes its substrate site-specifically[18], thereby avoiding excessive degradation of the protein. Ca2+ permeability within the sarcoplasmic reticulum is altered during exercise and may thus play an indirect regulatory role, but studies of the effects of exercise and nutrition on this enzyme have not been reported in the field of sports medicine.

4.3 Synergistic effects of exercise combined with nutritional supplement on protein metabolism

Both exercise and nutrition play important interventional roles in promoting skeletal muscle protein synthesis, and reducing its mass loss, and are recognized as effective in preventing and treating muscle atrophy, but it remains controversial whether combined interventions of the two can complement each other and synergistically contribute to the amelioration of Sarcopenia. It has been proposed that exercise combined with dietary amino acid/protein supplementation can have a "double whammy" effect in improving myasthenia gravis[22].

The effects of the dual intervention of exercise and nutrition may have more diverse mechanisms, perhaps co-regulated by both positive and negative facilitation or inhibition. Exercise helps to turn the body's blood circulation and increase the absorption of nutrients, which is conducive to protein anabolism; however, it has also been found that exercise requires an energy supply, so it may not be conducive to muscle protein synthesis, and overtraining reduces the total protein content of skeletal muscle[32], and even accelerates the catabolism of skeletal muscle proteins to satisfy the energy demand

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during exercise. Therefore, choosing the right type of exercise, as well as supplementing with the necessary nutrients at the right time, becomes necessary to promote protein synthesis and reduce degradation, especially in older age groups.

Nutritional supplementation has also been shown to improve the repair of muscle damage and protein metabolic imbalances associated with athletic training. Studies have shown that muscle strength and muscle protein synthesis levels in older adults achieved more significant results after strength training combined with fish oil supplementation interventions than fish oil supplementation alone [33].

5. Conclusions

In summary, Sarcopenia, which accompanies aging, is characterized by a reduction in skeletal muscle mass and a decrease in skeletal muscle function, which can adversely affect the physical health and level of social activity in the elderly population. Scholars have worked tirelessly in reversing the symptom and exploring the mechanisms of its development, and have found that an imbalance in skeletal muscle protein metabolism is directly responsible for the development of Sarcopenia. In the study of interventions to promote synthesis and inhibit degradation, exercise, and nutritional interventions have positive effects, especially the promotion of protein synthesis by leucine and resistance exercise has been unanimously recognized by the relevant experts, but the specific mechanism of action is not yet clear, and the effect of the combined intervention of the two as well as the impact on protein catabolism are still relatively few research reports.

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