

REVIEW

Motor unit changes in normal aging: a brief review

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Abstract

Aging is explored by multiple lines of research, in a pursuit of understanding this natural process. The motor response is usually the main dependent variable in studies regarding physical or cognitive decline in aging. It is therefore critical to understand how the motor function changes with age. The present review, aims at presenting briefly some of the most recently published works in the field, focusing on the three key components of the motor unit. The changes that the skeletal muscle undergoes aging sarcopenia, alteration of fiber type distribution and also intimate metabolic transformations. The neuromuscular junction suffers at cellular and molecular level, with possible implications of various cell components, mediators and oxidative stress. Motoneuron loss and change in their physiological properties accompany remodeling in the motor units. The applicability of knowledge in this field lies in possible interventions intended to counteract these age-related losses.

Keywords: motor unit, aging, neuromuscular junction, skeletal muscle, motoneuron.

Introduction

Recent changes in the structure of the population and estimations suggesting demographic aging, of which Romania is no exception, may justify the researchers' current interest for the aging process. Part of normal development, age-related motor decline seems to be the end result of multi-factorial causes, of which muscles and central and peripheral nervous system play their role.

This comes to justify why aging is explored by multiple lines of research, in a pursuit of understanding this natural process. The motor response is usually the main dependent variable in studies investigating physical or cognitive decline in aging. It is therefore critical to understand how the motor function changes with age. As the foundation of the motor system, the motor unit bears a lot of importance in the study of normal aging. Aging brings alterations in muscle, neuromuscular junction and motor nerve, in terms of both morphology and function.

Far from being an extensive work, or ever intending to be so, the present review, aims at presenting briefly some of the most recently published works in the field, focusing on the three key components of the motor unit.

Neuromuscular changes in elderly

Age-related alterations in neuromuscular system are recently seen [1], as caused by functional denervation, muscle wasting, and weakness, with hormonal changes, oxidative stress and mitochondrial dysfunction playing a major role [2, 3]. Given that "by the age of 70, the cross-sectional area of skeletal muscle is reduced by 25–30% and muscle strength is reduced by 30–40%" [4, 5], it is

only natural to expect changes in the skeletal muscle as underlying mechanism of age-related decline. All the more recent animal studies indicated that loss of muscle mass precedes age-related denervation of myofibers [6, 7]. Whether or not skeletal muscle is the *primum movens* of motor system aging is still arguable, but, unquestionably neural involvement is at least partly responsible [8]: motor cortex modifications [9], spinal and cortical excitability decrease [10], reduction of motor units [11], motor axon conduction velocities decrease [12].

Skeletal muscle alterations

Skeletal muscle undergoes changes that may be caused by aging, disuse and disease, sometimes being a challenge to differentiate between these factors. Regardless, findings of progressive loss of muscle mass, concurrent with loss of muscle function are documented.

Muscle morphology, neurologically determined atrophy, protein balance disturbances (due to mechanisms involving insulin growth factor 1 or other inflammatory factors, oxidative damage or intrinsic changes [13]), muscle tendon stiffness, all lead to clinical manifestations of sarcopenia: loss of muscle power and mass, and derived risk factors [14].

Much investigated, aging sarcopenia is a condition assuming progressive muscle loss with advancing age, associated with functional failure derived from this loss. Epidemiological studies give different values for the prevalence across age within populations depending on the operational definition, upon which only recently consensus definitions of 'sarcopenia' have been established [15–17]. It is not necessarily correlated with body weight, although sarcopenic obesity correlates with loss of muscle

mass [18]. Besides obesity, sarcopenia is associated with other major co-morbidities such as osteoporosis [17, 19] and type 2 diabetes [20, 21]. The etiology of sarcopenia is multifactorial and can include physical inactivity, altered endocrine function, chronic diseases, inflammation, insulin resistance, and nutritional deficiencies [16, 22]. The risk factors for sarcopenia are extensively described in literature, and include age, gender and level of physical activity [23, 24]. A particular aspect in the development of sarcopenia is the short-term disuse atrophy, since it has been suggested that different short periods of muscle disuse, due to injury or sickness (elderly are very vulnerable to both) contributes considerably to the net muscle loss observed with aging [25].

Fiber distribution alteration, with the predominance of muscle fibers type I [26], may not be a general rule. No significant changes in fiber type distribution, with increased average type IIa fiber diameter was reported, though the authors question this finding. The same longitudinal study, though discovering significant loss in muscle strength and reduction in muscle cross sectional areas in anterior muscles of the thigh, but not the posterior compartment, reported no decrease in single fiber maximal force or specific force in both types of fibers, a finding reported for the first time [27].

Progressive decrease in anabolism with increase of catabolism results in muscle force decrease and power decline, as well as reduced muscle regeneration capacity. Among the responsible causes may be neuropathic, hormonal, immunological, nutritional and physical activity factors [18, 28], with recognized gender-related differences: men show gradual decline, whereas women's muscle mass and function seems to suddenly drop after menopause [28]. The underlying mechanisms of these losses include shifts in muscle protein turnover, tissue remodeling, loss of alpha-motor-neurons, muscle cell recruitment changes and apoptosis [28, 29]. Age-related atrophy mechanisms have apparently direct application on maintenance of neuromuscular junction [30].

Another recently published review [31] focused on the metabolic pathways and mediators of muscle wasting, as exemplified in aging sarcopenia and cachexia, at the tipping point between increased catabolism and decreased anabolism. However, the factors involved in the etiology of cachexia (proinflammatory cytokines, hypermetabolism and malnutrition) are very different from those behind sarcopenia (hormonal changes, physical inactivity and neurodegenerative alterations) [32]. Among the main mechanisms at fault for muscle reduction are a sedentary lifestyle, endocrine or neuromuscular dysfunction, alterations of protein intake or metabolism, and even changes in gene expression [31, 33]. Note that is not merely a quantitative muscular loss, but qualitative mechanism may have their involvement as well, as single fiber muscle properties may change without changes in myosin content [34].

Aging muscle metabolism undergoes several other changes as well. If decline in anaerobic power seems to be affected more than aerobic power [35], there is evidence of the preference for oxidative energy production, and less for glycolysis, though the glycolytic pathway seems not to be affected by age, avoiding thus the accumulation

of metabolites and reducing the energy costs [36]. Higher aerobic capacity allows greater aerobic reserve, which in turn, is associated with higher physical performance capacity in elderly [37]. Although the relationship between serum creatinine levels and muscle functional limitation is complex, correlation between the two parameters was proven in the case of the participants in the *Study of Physical Performance and Age-Related Changes* [38].

Recently discovered in nematode and identified in vertebrates and humans [39] miRNAs modulate multiple biological processes underpinning cell development, growth and death [40]. Despite it is known that the human genome contains over 1500 miRNA genes [41] and that each miRNA can regulate a large number of mRNA targets, very little is known about his specific role in gene regulation because only a few miRNA targets have been particularly experimentally analyzed [42]. MicroRNAs (miRNAs) modulate gene expression in skeletal muscle, and are associated with aging. Although several hundred miRNAs are detectable in skeletal muscle, specific miRNAs termed myomiRs, are preferentially expressed in myoblasts and myotubes [43].

Muscle decline has been looked at mostly in late years of life, but additional focus on early characteristics is justified under the light of developmental modulation of the human muscle. However, little research has been done in the direction of linking early environmental influences with molecular and cellular changes in human muscle, although size at birth seems related with muscle size in older men. The direct implication would be a lifelong approach in managing sarcopenia [44].

☞ Neuromuscular junction

Neuromuscular junctions play a very important role both for the muscle and the motor nerves. Reviewing the cellular and molecular changes of the neuromuscular junctions, Jang and Van Remmen synthesize that “degeneration of motor neurons is followed by changes in structural and functional integrity of the neuromuscular junction (NMJ)” [1]. Animal model systems have led to a better understanding of the aging process at this level, bringing proof of functional denervation dependent on muscle activity or fiber type, changes in endplate size, terminals, sprouts, and synaptic vesicles. Exploration at subcellular level revealed that the presynaptic component may suffer in aging from decline in synaptic vesicles and mitochondrial content, with increase in endoplasmic reticulum, coated vesicles and cisternae. These last changes may be involved in calcium sequestration and neurotransmitter release. Increased turnover of neurotransmitter and defective axonal transport furthers the functional impairment of the neuromuscular junction. Another responsible factor seems to be the decrease in terminal Schwann cells, with widening of the nodes of Ranvier. At a molecular level, brain derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), neurotrophin-4 (NT-4), cytokines and other growth factors are modulators of neuromuscular system to a different extent in aging [1].

Oxidative stress seems to have a questionable role. From the oxidative theory of aging, it would result that

decrease of oxidative stress, by decreasing oxidant aggression or increasing antioxidant response or a combination of both, should increase life span. In the skeletal muscle, potential sources of oxidative species have been blamed on the mitochondria [1, 45–47], cytosol and membrane, the subject of comprehensive recent reviews [48, 49]. Concerns for the need to correct subsequent progressive functional loss of the muscular system have also been expressed [50, 51] the solutions currently provided varying from non-specific antioxidants, such as vitamin C, to correction of the oxidative signaling pathways.

The question, that needs answering, concerns the involvement of oxidative stress in aging or healthy aging. A synthesis of the results on animal studies on knockout or transgenic mice, with one or more of the antioxidant enzymes (superoxide dismutases, glutathione peroxidases, thioredoxins) found little support for the contribution of oxidative stress to aging, as measured by life span [52]. The reduction of the life span in the study groups was mostly attributable to a worsening of the pathologies the mice developed. A possible explanation would be that oxidative stress does not affect aging, but progression of disease, or that its role depends on the environment, meaning that it only influences life span under conditions of chronic stress. This new promising view contradicts the classic observation of involvement of oxidative stress in aging, currently rising more questions than offering answers.

The latest concerns as far as aging muscle function goes have been focused on Ca^{2+} as a key ion in many physiological processes located in the muscle and at the neuromuscular junction. Ca^{2+} sparks are pulsatile signals important to excitation-contraction coupling, as well as an index of the capacity of the muscle to maintain the homeostasis of this ion and describe the status of signaling. Aging is associated with a loss in the plasticity of the Ca^{2+} sparks due to defective calcium release, and membrane structure. This hypothesis may be the base of future treatment therapies, concentrated at this molecular level [53].

☐ Motoneuron changes

The aging process is presumed to affect motor units by loss of motoneurons, apparent increase in slow twitch fibers, atrophy of the denervated fibers or reinnervation by neighboring fibers, generating a remodeling of the motor units by denervation – reinnervation cycles. Following this line of research, motor unit size and the threshold force for recruitment were assessed by macro-electromyography in first dorsal inter-osseous muscle, a hand muscle with approximately equal proportions of fast-twitch and slow-twitch muscle [54], and the tibialis anterior muscle, with mostly slow-twitch fibers [55]. Though the expected increase in motor unit size is suggested by the greater amplitudes the elderly registered, the size principle of motor unit recruitment is preserved. Motor unit size/recruitment threshold relationship is preserved by three possible mechanisms according to the previously mentioned authors: reinnervation of fast-twitch fibers by small, or by “mid-sized” motoneurons, or

a global decrease of all motoneurons, without excluding the morphological changes the motor unit can undergo.

Also, it seems that activation pattern does differ in old by comparison to young according to a study on the changes in Hoffmann-reflex excitability depending on age and type of contraction. Based on the results obtained from performing isometric, concentric and eccentric plantar flexions, the researchers suggested that the young would use similar activation strategies regardless of the type of plantar flexion, whereas the old would resort to synergic muscle contraction [56].

Excitability of motor neurons, either central or peripheral, is age dependent, most of the excitability indices being slightly altered with age: slightly longer strength duration time constant, smaller late depolarizing threshold electrotonus, smaller supernormality and smaller threshold changes in the current–threshold relationship for both depolarizing and hyperpolarizing currents [57, 58]. The *Baltimore Longitudinal Study of Aging* found age dependent motor unit size, firing rates [59], maximal firing rates differences in aging having been documented as well [60]. The explanation lies in altered axon metabolism, some of the mentioned indices being explained by persistent sodium channels, which increase with age [57, 61]. However, extraneural factors, such as tissue impedance and gender differences, should not be overlooked.

Spinal cord neural circuitry has control over muscle activation. Studying to what extent the aging process affects this mechanism, according to Monaco *et al.* concluded that age-related changes of the motor and nervous systems lead to old age-modified integration of information like biomechanical requirements, peripheral afference and descending inputs at spinal level. Motor primitives, muscle synergies force generators, “synchronize” muscle activation mainly depending on the biomechanical demand of the locomotion; hence, they are not significantly affected by aging” [62].

On the same note, distortion of the adjustment between primary sensorimotor cortex and motor neuronal pool is likely to contribute to a reduction in motor control in elderly [63]. All the more since “functionally relevant specialization of lateral spinal cord white matter, and an increased sensitivity to age-related decline in medial spinal cord white matter in healthy subjects” characterizes old age [64].

☐ Motor unit firing

Healthy aging of the motoneuron was also assessed with respect to its function.

Studies on motor unit firing rates variability produced rather contradictory results, some showing significant differences between the young and old, some not reaching statistical significance. Knowing that high motor unit-firing rate may be responsible for lower force steadiness, which characterizes the elderly [65, 66], a study [66] aimed at comparing older and younger subjects by collecting information on the index and thumb during a pinching task. According to the authors, firing rate variability plays a key role in improving force steadiness, unlike motor unit synchronization, which did not seem to play a part. The same study showed, by before and after short-term light-load training comparison (meant

to improve force steadiness by reducing firing rate variability), that motor unit firing rate variability reduces with training in older subjects, though initially being similar in elderly and young, in this particular study.

Decreasing motor unit firing rates with increased variability characterize muscle fatigue, of which the elderly are expected to be, to some extent, protected due to the predominance of type I muscle fibers in the senescent muscle. Analysis of motor unit firing behavior during submaximal 50% maximal voluntary contraction (MVC) prolonged contraction of tibialis anterior found slight but not significant differences between young and old in time to task failure, motor unit firing rates and firing rates variability. Reporting for the first time doublet motor unit discharges (two action potentials generated close in time in order to enhance muscle force) in older adults [26], the study also confirmed the existence of motor unit firing cessation, explained as a compensatory mechanism, respecting the size principle of the motor unit recruitment. The possibility of muscle fatigue resistance being muscle dependent was discussed, as well as the contribution of neural component in adapting to force-requiring task.

Individual muscles firing rates have a slower twitch contractile speed and contractile properties, showing lower mean maximal motor unit firing rates (MUFRs). These neuromuscular findings apply for triceps surae, but the situation seems to be slightly distinct for soleus muscle, the authors concluding that individual muscle properties might not apply for whole muscle in this particular case [67]. It seems that “at least for proximal upper limb muscles, mean maximal motor unit discharge rates reductions with healthy adult aging are muscle specific and not strongly related to contractile speed” [68].

MUFRs and maximal voluntary force were also investigated in the dorsiflexor muscles of the foot in terms of age- and training-related adaptations, along with motoneuron after hyperpolarization. Although baseline examination proved superior values in the young group, after training, assessment indicated that “age-related” changes underwent a short-termed adaptation, making them comparable with values specific to the youth [69]. Nonetheless, motor neuron recovery rates and consequently contractile properties are delayed in old, in contrast with young, although both young and old suffer an important fatigue-induced reduction in MUFRs, as a study on soleus muscle shows [70].

On the other hand, it has been shown by comparing the number of functional motor units of the muscle tibialis anterior of “master runner” aged people, with healthy age-matched controls, and recreationally active young that aged people seem to benefit from life-long intense physical activity. Motor unit number estimates of masters’ runners and young were both higher compared to the old [71]. The idea started from a similar animal model, the testing on humans being a first, to our knowledge. Another comparison between sportsmen and untrained, made during incremental exercise on a cycle ergometer, proved that older persons’ muscle fiber conduction velocity (MFCV) does not increase with the intensity of exercise, the maximal MFCV in untrained old being significantly lower than that of young, trained or untrained. Since MFCV correlated with cardiovascular indicators in the

young, the questions that arises concerns the strategies of motor units recruitment [72].

Improving theoretical knowledge is also reflected by mathematical modeling of age-related neuromuscular changes. This has given insight on recruitment, rate-coding, and force output in motor units, with direct applicability in understanding aging. The Heckman–Binder model applied on human quadriceps motor units [73] proved that elderly can reach around 50% of the force levels attained by younger individuals, with relatively similar or even slightly lower input.

Final considerations

Senescence, as a biological process assumes morpho-physiological changes, which ultimately lead to functional deterioration, motor alterations having a major impact on the quality of life. In the context of current demographical aging, the focus on normal aging is to be expected.

Current literature concurs that even the healthiest seniors’ experience alterations of the cognitive and motor functions. Age-related alterations of the peripheral and cortical neural motor functions are part of the underling mechanism of motor aging, alongside skeletal system decline.

The applicability of knowledge in this field lies in possible interventions intended to counteract these age-related losses, directed at physical exercise, medication, assistive devices, and social involvement.

Physical interventions have a positive effect on functional status [74]. Its benefits in maintaining motor function are doubled by cognitive improvement, a very important desiderate, especially since a connection between memory retrieval and motor actions, as well as influence on positive or negative life experiences, has been proven [75]. Regardless, the simple reasoning behind this method is the principle “use it or lose it”. Physical exercise interventions, in most of the cases submaximal [76] are beneficial at delaying aging, effects like stopping or reversing aging being highly questionable.

Medication intended to ameliorate motor deficits are targeted in multiple directions: dopaminergic and cholinergic transmission [77], anti-inflammatory drugs [78], diet [79], caloric restriction-simulating drugs [80], hormones [81–84], and vitamins [85, 86], with conflicting results.

Recently, robotic devices have been designed to accustom the needs of elderly. Also, technology-enabled cognitive training is tailored to address the cognitive decline [87, 88].

Social interaction plays an undeniable role, community dwelling adults having multiple benefits by comparison with their institutionalized counterparts [89].

All these methods have as ultimate goal to ensure not only a longer lifespan, but most important, a healthier, more fulfilling lifestyle besides the biopsychosocial challenges that old age brings. Knowledge about successful aging has expanded greatly, but general agreement on how successful aging can be achieved has not yet been clarified.

Author contribution

All authors have equal contribution.

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