MINIREVIEW

The Physiology and Biochemistry of Skeletal Muscle Atrophy as a Function of Age (43727)

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Abstract. **The skeletal muscles are an important entity in the proper function of aging animals and humans. Studies have shown that until humans are 60–70 years old, age-related changes in muscle function and structure are relatively small, while after 70 years, these alterations are accelerated considerably. Factors responsible for the "aging" of skeletal muscles are complex and include intrinsic biochemical changes in muscle metabolism, changes in the distribution and size of muscle fibers, and a general loss of muscle mass. In addition, other factors like the control of muscle contraction by the motor neural system and the influence of external conditions such as exercise, immobility, nutrition and others may also contribute to the age-related decrease in muscle functions. Studies have shown that with age there is some loss of peripheral motor neurons, reduction in the number of motor units, alterations in the neuromuscular junctions, and selective denervation of Type II muscle fibers. These findings led to the concept of denervation atrophy of skeletal muscles as one of the major mechanisms for muscle degeneration in old age. However, it should be emphasized that the extent of age-related changes varies from muscle to muscle, and some do not seem to be affected by age. For example, it has been shown recently, in animal studies, that weight-bearing muscles are much more susceptible to senescent processes than non-weight-bearing muscles. More work is needed to clarify the contributions of the various factors, especially the role of muscle training in alleviating the symptoms of age-related muscle atrophy.** [P.S.E.B.M. 1994, Vol 206]

The body of knowledge accumulated in the last century concerning the structure and function of skeletal muscles is enormous. This knowledge has been used for many years for a variety of human needs, such as improvement of athletes' sports activities, medical treatment of various diseases, and other psychosocial aspects of human life. It is now quite accepted that with advanced age there is a general decline in certain muscle functions. This reduced functionality has been attributed to a number of changes that have been observed in the muscles of old humans and animals. Understanding the changes that take place in muscles of aging humans is especially important for clinical treatments of old people, as well as for the improvement of the quality of life in advanced age.

The changes that have been observed in aging skeletal muscles are on several levels, such as bio-

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chemical, morphological, and physiological, and are especially pronounced in old people who are quite immobile. This phenomenon has been termed *disuse muscle atrophy,* and it is typical of muscles of the lower extremities of old people. The weakness of the lower limb muscles contributes to the well-known phenomenon of increased falls and decreased stability of aging individuals.

The mechanisms and etiology responsible for the age-related changes in muscle physiology and function are quite complex and not well understood. However, three areas which have been actively investigated in the last several decades will be discussed in this review: (i) the contribution of intrinsic biochemical and physiological changes to muscle atrophy in old age; (ii) the importance of the neural system; and (iii) the influence of external and environmental factors such as exercise, disuse, nutrition, and disease to the well-being and proper function of skeletal muscles in aging organisms. A general outline of these main areas is depicted in Figure 1.

Changes in Muscular Apparatus With Aging

Molecular and Biochemical Changes. Several excellent reviews on the subject of muscle aging have been written in the last decade (1–7). The discussion in this review will start with the molecular and biochemical level, since changes on this level are probably some of the first events in the cascade of processes leading to muscle atrophy with old age.

Protein metabolism. Protein metabolism in aging humans was the subject of a recent review (8), which reported that with aging a progressive loss of total body proteins, attributed largely to loss of skeletal muscle proteins, was observed. While muscle mass was estimated to account for 30% of whole body protein turnover in young adults, this value was only 20% in elderly subjects (8). Indeed, studies of young, adult, and old Sprague-Dawley rats showed a marked decline with age of total muscle sarcoplasmic reticular proteins as determined per gram of muscle tissue (9). The reduction of protein turnover and synthesis has been observed in other tissues, like the liver, brain, and kidneys of aging animals (10, 11). This decline in muscle protein content with age will be discussed later in conjunction with the known loss of muscle mass and loss of fiber size with advanced age.

Muscle enzyme activities as a function of age. Early studies on the level of activity of actomyosin ATPase, the enzyme responsible for the provision of energy for muscle contraction, showed a marked decrease of activity in striated muscle of aging insects (12) and rats (13). Similar results were reported by Kaldor and Min (14). Interestingly, this decline of myosin ATPase was correlated with the reduced speed of muscle contraction observed in old age (13). Indeed, previous studies by Barany (15) have shown that the level of myosin ATPase activities could be correlated with the speed of muscle shortening. However, recent studies by Florini and Ewton could not find any difference in the activity of myosin ATPase in muscles of aging animals (16). The reason for the discrepancy with the above results is not clear, but Faulkner *et al.* (2) correlated the apparent lack of change observed in

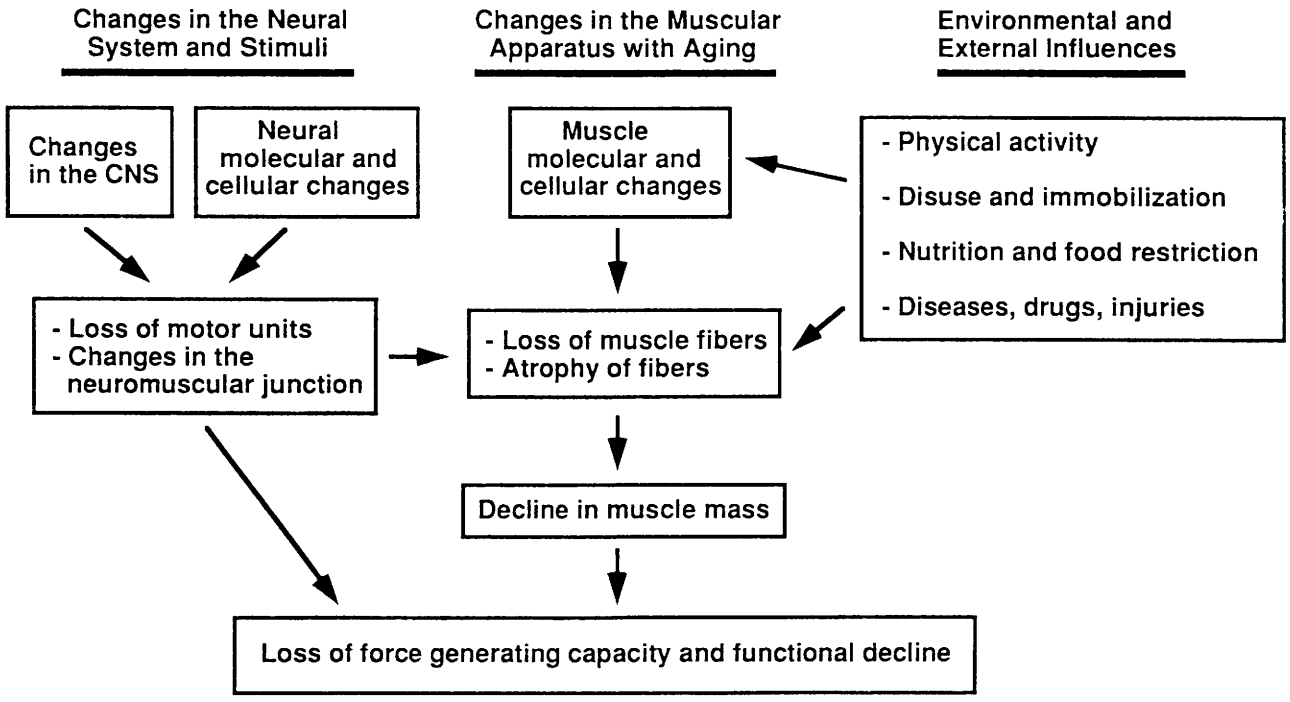

FIGURE 1. Possible factors contributing to age-related changes in muscle structure and function.

ATPase activity in old age with the observation that the intrinsic velocity of shortening of the whole muscle also did not change with aging.

Another enzyme involved in the ATP regenerating system is creatine phosphokinase (CPK) and several isoenzymes existing in mammalian systems. Among them, the MM is the predominant isoenzyme in the skeletal muscle. Reports on the decrease in muscle CPK activity in aging humans (17) and mice (18) appeared in the literature. However, Ermini (19) could not show in previous studies any significant change with age. Later, studies by the same author did show that phosphocreatine (PC) and ATP contents were decreased significantly in skeletal muscles of aged Wistar rats and that the capacity to restore PC was diminished considerably in skeletal muscles of old rats (20). However, Klitgaard *et al.* (34) reported no change with age of levels of ATP and PC, but did find lower concentration of glycogen in aging gastrocnemius muscle. Thus, reports on the enzymes involved in muscle ATP hydrolysis and restoration are conflicting. This may be due to the different muscles or animals used by the various investigators.

Muscle aging has been associated with the decline of other enzymes involved in energy metabolism. Thus, some enzymes of the glycolytic pathway, like aldolase (21) and lactic dehydrogenase (22), were shown to decrease in activity in aging rodents. Some reports also showed that mitochondrial enzyme activities are decreased in muscles of aging animals (23, 24). However, recent comprehensive studies by Holloszy *et al.* (25), on glycolytic and mitochondrial enzymes of the three different types of muscle fibers of old rats, demonstrated that the decrease of the enzyme activities is quite different in the various types of skeletal muscles. In these studies, the greatest decrease of glycolytic enzyme activities was observed in muscles containing Type IIb and Type IIa fibers, which are more anaerobic in nature. In the soleus, which contains mainly Type I oxidative fibers, only the terminal enzymes of glycolysis, like pyruvate kinase and lactate dehydrogenase, showed a significant reduction in old muscles (25). Similarly, the reduction of mitochondrial enzyme activities, both of the Kreb cycle and the respiratory chain enzymes, was very pronounced in the red (oxidative) soleus, they were mildly reduced in the mixed fibers type muscle, like the plantaris, and no significant change in activity was observed for the white portion of the vastus lateralis muscle. The important conclusion drawn from the above results is that enzyme decline in muscles of old animals depends clearly on the function and presence of these enzymes in the various muscles composed of different fiber types, a point which was not addressed in previous studies on enzyme activities by other investigators.

Alkaline phosphatase (ALP) was shown recently by histochemical methods to be present in the outer layer of the sarcolemma membrane of striated muscles (26). Studies on the cysteine-sensitive portion of ALP, which is mostly membrane bound, showed a significant decrease in gastrocnemius muscles of old mice (27). On the other hand, in bicarbonate-extracted muscle, which represents the aqueous form of the enzyme, a complimentary increase of cysteine-sensitive ALP activity was observed (27). Similarly, an increase of acid phosphatase (ACP) activity in the gastrocnemius muscles of aged mice was also reported (28). This later study may imply that in aged muscles there is an increase in catabolic activity of lysosomes as represented by muscle ACP activity.

Some other biochemical changes. On the average, connective tissue constitutes only about 2% of the total cross-sectional area of the muscle fibers (2), and the increase in concentration of connective tissue in skeletal muscles from adult to old animals has been estimated in the range of 20%–40% (29). Concomitantly, collagen content of muscle fibers is elevated with age with an increase of 40% in fast (Type II) fibers and 30% increase in slow (Type I) fibers (30). However, other workers observed a higher increase of collagen content in Type I fibers than in Type II fibers (31, 32). This increase of collagen content was correlated with changes in stiffness of muscles observed with age (31, 32). Biochemical studies showed that collagen from old muscles is less susceptible to collagenase degradation and the activity of the enzyme was reduced significantly with age (30).

Interestingly, a study on the content of myoglobin of aged rats was performed by Beger and Fattore (33). In this study, the content of myoglobin in rats from 2, 5, 9, and 25 months of age was found to increase up to 5 months and remain constant between 9 and 25 months of age. Four months of endurance exercise beginning at 21 months increased substantially the old (25-month) muscle content of myoglobin (33).

The significance of skeletal muscle tissue as the main target for insulin resistance observed in advanced age has been a subject of considerable research in the last few years (35–38). Early studies by DeFronzo *et al.* (35) on humans have shown a marked reduction of glucose metabolism with age which was attributed to peripheral tissues (35). A subsequent study has suggested that the muscle tissue is the main target for this decrease of glucose disposal with age (36). Similar studies in rats have corroborated the above results in rodents (37). However, more recent studies by Ivy *et al.* could not find any difference in glucose uptake by hindlimb muscles of young, middle age, and aging 24-month-old rats (38). The authors of this last report have criticized the previous results obtained in rodents, emphasizing that relatively young—not really aged—animals were used in the previous

studies (37). The final conclusion put forward by Ivy *et al.* was that ". . . our findings argue against the concept that aging results in skeletal muscle insulin resistance in rats" (38).

A very important biochemical event in muscle function is the initial excitation of muscle sarcolemma membrane leading to the eventual contraction of muscle myofilaments. This event is mediated via release of calcium ions from the cisternae of the sarcoplasmic reticulum (SR), binding the calcium to the troponin molecules on the actin filaments and initiating the ATP dependent muscle contraction. Eventually, these calcium ions are resequestered by Ca^{++} Mg^{++} (SR) ATPase, resulting in muscle relaxation. Studies by Gafni and Yuh (9) have shown that although the activity of Ca^{++} Mg^{++} ATPase was not changed with age, there was a considerable decline of Ca^{++} ion reaccumulation in the ST vesicles. When the rate of Ca^{++} transport was compared with the rate of ATP hydrolysis, there was a marked decline in the ratio Ca^{++} transport:ATP hydrolysis. However, previous studies of the ratio Ca^{++}: ATP in muscle sarcoplasmic reticulum did not observe this age-related decline (39).

The conflicting findings which characterized most of the biochemical studies described above emphasize the point that biochemical changes observed on the energetic, enzymatic, and other levels are not universal phenomena in all muscles of aged animals. They may depend on the type of muscle examined, on the conditions of the animals, and on the influence of the other systems external to the muscular apparatus.

Cellular and Morphological Changes. *Changes on the ultrastructural level and accumulation of lipofuscins.* Electron microscopy studies conducted on skeletal muscle biopsy specimens of elderly people with no evidence of neurological or muscular diseases revealed some histological changes that were quite evident in old age (40). Overall, the general architecture of muscle was well-preserved. There was some focal myofibrillar degeneration with distortion of the Z lines. There was also some single fiber atrophy in some individuals and a very small increase of fatty and connective tissues. The most striking feature of aging muscles was the accumulation of lipofuscin granules, also known as age pigments. These were found in the subsarcolemmal regions, near the nuclei and occasionally within the satellite cells. These granules, which are known to accumulate with age, have also been found in brains, livers, and hearts of aging animals, and are believed to originate from lysosomal residual bodies (40). They are considered to be products of damage to intracellular membranes due to lipid peroxidation processes. Similar ultramicroscopic studies by Gutmann *et al.* on rats (41) and Lutatscher *et al.* on mice (42) revealed a marked proliferation of the T tubule system with accumulation of ribosomes in aging muscle fibers (41). In mice of 27 months, an abundance of lipofuscin pigments was observed, with disruption of the sarcomeres and dislocation of the Z lines. Some increase of perimysial collagen was also observed. Forced short-term exercise on these animals resulted in an increase in T tubule systems of the sarcoplasmic reticulum. Overall, the conclusion of most researchers is that most of the architecture of aging muscle is well preserved in old age with some minor but probably significant changes characteristic of old age (42).

Changes in muscle fiber number and types. Early studies in the 1970s and early 1980s reported that with age there is a decrease in muscle fiber number and no apparent change in fiber size (1, 43–47). These results were obtained for mouse and rat soleus, extensor digitorum longus and diaphragm muscles (1, 43–45). Similar observations were also reported for the rectus abdominus (46) and vastus lateralis (47) of humans. But other workers have shown that counting all the fibers in a cross-section of a muscle may not represent the total fibers of a whole muscle (48, 49). Thus, Maxwell *et al.* (48) and Gollnick *et al.* (49) have shown that counting these fibers in the midsection of a muscle may result in an erroneously low number, as not all fibers extend from tendon to tendon. Indeed, Brown has raised doubts about the validity of the earlier studies using midsection samplings of fibers (50). In her studies, which used the technique of muscle digested in nitric acid, no change in fiber number of soleus and extensor digitorum longus muscles was observed for rats aged 6–24 months. The conclusion was drawn that change in fiber size leading to atrophy, not to fiber number change, occurs with aging. Similar observations of no change in fiber number with aging were reported for muscles of mice (51), rats (25), and humans (52). The question as to the relative composition of the three main muscle fiber types, Type I (the slow twitch) and Types IIa and IIb (the fast twitch), in aging has also been a subject of some controversy. Probably, the most consistent finding has been that with advanced age there is a relative decrease in Type II fibers (53, 54). Nevertheless, other researchers could not confirm these results (47, 55). Moreover, Silbermann *et al.* (51) even observed a significant increase with age of the percent of Type IIb fibers in the rectus femoris of old mice, with concomitant decrease of Type I fibers.

The controversy regarding whether muscle fiber change in numbers or in size with age has been lingering in the literature, and recently an important work has shed some light on this issue. Holloszy *et al.* (25) examined two groups of muscles in aging male rats: weight-bearing muscles and non-weight-bearing mus-

cles. Atrophy and muscle weight loss were observed occurring mostly in the weight-bearing muscles containing a high proportion of Type IIb fibers, like the quadriceps, gastrocnemius, and plantaris muscles. On the other hand, non-weight-bearing muscles like epitrochlearis and adductor longus did not lose any significant weight with age (25). The important conclusion drawn from the above work is that age-related changes may be manifested differently in the various muscle fiber types and also may depend on whether the muscles in question are weight-bearing or non-weight-bearing.

Physiological Changes with Age

Decrease of Muscle Size, Mass, and Strength with Age. It is generally accepted that muscle size and mass are reduced with age (1). Moreover, the loss in size and mass could be correlated with the decline in muscle strength with age. In a study by Young *et al.* (56) using the ultrasound technique to measure the cross-sectional area of the quadriceps muscle, a 25% decrease of quadriceps size was observed for people in their 80s, compared with people in their 20s, with a 39% reduction of isometric strength of the quadriceps of old people. Similarly, using computer tomography, the size of the leg muscles was found to be smaller in 28%–36% in aged people over 65 years (57). Indeed, as was illustrated by Faulkner *et al.* (2), the maximum isometric strength from age 30 to above 80 is reduced, on the average, by 30%–40% in people where the loss of strength in leg muscles is about 40%, compared with 30% in arm muscles (2). Vandervoort (4) has accumulated 18 different studies from 1947 to 1988 of various muscles in which isometric strength has been shown to decline by 25%–55% in elderly people from 60 to 70 years old. Reed *et al.* (93) have found a significant age-related decrease of muscle strength per unit of lean body mass which could be correlated highly (r = 0.79) with cumulative muscle strength in aged people. However, they have cautioned against using clinical measurements of lean body mass to predict muscle strength. In rodents, there has been some controversy regarding whether maximum isometric force, which is equated with muscle strength, does change with age. While McCarter and McGee (58) could not find any change in this parameter in aging rats, other workers have reported a decrease of 20% in the soleus and extensor digitorum longus muscles in aging mice (59) and rats (60).

Since it is unclear whether or not the decrease of fiber size is accompanied by a decline in fiber number with age, it remains possible that both types of changes may contribute to the observed reduction in muscle mass in advanced age. This diminution of muscle weight with age will result eventually in loss of force-generating capacity and other functional capacities in aged muscles (Fig. 1).

Changes in the Muscle Power Output with Age. The power output of muscles has been defined as the average force developed by muscles multiplied by the velocity of shortening (2). As one might expect, the velocity of shortening differs considerably between slow and fast twitch muscles. However, in either type of muscles, no substantial changes in the velocity of shortening were observed in aging animals (59). But when power output was determined for various force measurements, a 69% reduction was obtained for old mice. Normalizing these values per muscle mass, which is generally reduced in aged animals, resulted in a decrease in normalized power output in old mice (61). Thus, the changes in muscle mechanics with age are very complex and ill understood. These changes probably involve changes in the delivery of adequate blood supply (capillarization), in oxygen consumption, and in the capability to maintain proper energy balance. Some of these conditions, which are impaired in old age, would affect the mechanical functions of the aged muscle (2).

Changes in the Neural Control and Stimuli of Muscles in Old Age

Control by the Central Nervous System (CNS) and Changes in the Peripheral Motor Units. The central nervous system (CNS) controls the skeletal muscles' movements via two major networks of motor neural tracts: the pyramidal tract and the extrapyramidal tracts. While the pyramidal tracts originate in the cortex of the brain, the extrapyramidal neurons are controlled by the nuclei in the basal ganglia and the substancia nigra of the midbrain. Morphological and neurochemical changes of these aspects of the CNS have been described (62). Vandervoort and McCormass (102), in an attempt to ascertain the role of the CNS in controlling peripheral skeletal muscles of aging people, applied a brief percutaneous electric shock to CNS motor neurons. However, these elderly people of 60 to 100 years old were able to activate their ankle muscles maximally regardless of added CNS stimulus. Nevertheless, these researchers were careful to conclude that their study does not exclude the importance of the CNS in dynamic strength maneuvers involving many muscle groups (4). However, more specific information as to the mechanisms of CNS control of peripheral neurons in aging is quite lacking. Moreover, reports on altered structures and functions of peripheral motor neurons appeared in the literature (62) with some indication of a loss of motor neurons in the spinal cord with aging (6).

Single peripheral motor neurons may innervate a group of skeletal muscle fibers forming what has been

called a motor unit. These motor units can be categorized by morphological and physiological criteria into mainly two types: fast motor units (nerves that innervate the fast twitch Type II muscle fibers) and slow motor units (nerves that innervate the slow twitch Type I muscle fibers) (2).

As early as 1966, Gutmann and Hanzlikova (63), in their pioneering work, have shown that with aging there is a significant loss of total number of motor units in old muscles with remodeling of other motor units (63, 64). Later works by several investigators have shown that in aging skeletal muscle there is a decrease in the total number of motor units (65, 67) with specific loss of the fast motor units and a relative increase in slow motor units. Thus, Pettigrew and Gardinger (65) have shown that a typical plantaris muscle of young rats has 48 units, of which five to six were slow, while old plantaris consisted of 29 motor units, of which 11 were slow. This finding led to the conclusion that with aging there is a reorganization of the motor unit pool (67). Konda and Hashizume observed a decrease in the conduction velocity of old motor units along with a 30% decrease in the total numbers of motor units in the medial gastrocnemius of aged rats (66). Concomitant to the decrease in the number of motor units, there was an increase in the density of muscle fiber innervated by old motor units. The above workers, however, could not find a substantial difference in the distribution of fast and slow motor units, emphasizing the point that differential changes in slow and fast motor units may be specific for various muscles.

That the relative motor unit area increases with age while the total motor units decreases, supports the notion that with age the fast fibers may undergo denervation, and some may be reinnervated by sprouting nerves originating from the slow motor units (2). The latter observation is supported by the fact that, in muscles of aging people, there is a selective increase in fiber type grouping of Type I fibers while muscles of young people exhibit a heterogeneous mosaic pattern of fiber type distribution (1, 2). This last phenomenon of enclosed fibers and fiber type grouping has been interpreted as evidence for the denervation and reinnervation of the Type II fibers in aged muscles. Type II fibers that are not reinnervated will most probably degenerate and disappear (1).

Changes in the Neuromuscular Junctions. The neuromuscular junction (NMJ) is the crucial venue of the interaction between the neural and muscular systems. Any morphological, biochemical, and functional changes at this location will affect the capability of the muscles to respond to neural stimuli. There have been several interesting studies on age-related changes in the NMJ.

As early as 1965, Gutmann and Hanzlikova reported that there was a considerable fragmentation in the distribution pattern of acetylcholine receptors (AchRs) and acetylcholinesterase staining at the endplates of NMJs of old rats (68). More recent studies by Oda (69) have confirmed these earlier studies. Using intercostal muscles of humans (autopsied cases) of ages ranging from 32 to 76 years old, AchR distribution was shown to increase in number of smaller conglomerates. Also, endplate size increased with age with reduction of the percent of endplates that were innervated by unbranched axons (69). Rosenheimer and Smith have studied the differential changes of endplate architecture in different and diverse muscles of Fisher rats from 10 to 31 months of age. While soleus and extensor digitorum longus muscles revealed a decline in nerve branch sprouting in old animals, the diaphragm maintained the level of sprouting evident in young animals. However, changes were observed in the morphology of all three muscles, indicating considerable alterations in the endplate morphology in the 25-month-old rats (70).

Studies by Cardosis and LaFontaine (71) on the NMJs of soleus and diaphragm muscles of rats aged 5 through 111 weeks also revealed a dynamic ongoing remodeling of pre- and postsynaptic structures. With aging, there was a gradual and progressive loss of synaptic contacts, and at the older ages of 82–111 weeks, entire NMJs were lost (71). Finally, Ludatscher *et al.* examined the morphology of gastrocnemius NMJs of old mice compared with young ones and observed a variety of morphological changes in NMJs of old mice. These are illustrated in Table I. The most interesting finding, which was not observed in young animals, was the appearance of degenerated Schwann cells in the endplates of the old mice. Overall, while the young group had, in proportion, 85% of the normally structured endplates, this number was reduced to 40% in the old group (72).

The above studies in humans and rodents indicate that, although the NMJ is a very dynamic structure with axonal growth, sprouting, and regeneration capabilities, with age there are many signs that this remodeling process is shifting towards significant degeneration of the NMJs. This would affect the neural dependent muscular function of aging animals and humans.

The Influence of External Conditions and Environmental Factors

Effect of Exercise and Training. The effect of exercise and training on aging muscles has been the subject of numerous publications that will be beyond the scope of this review. Whether exercise has a positive or negative effect on muscles of aged animals and humans still remains a controversial matter.

Early studies on enzyme activities, such as aldolase (20) and creatine phosphokinase (73), of hind leg muscles of aging mice subjected to short-term (6-

Table I. Ultrastructural Evaluation of Motor Endplates of Young and Aging Mice[a]

	6-Month-old (No.)	27-Month-old (No.)
Motor endplate regions studied	48	60
Axon terminals counted in above regions	67	109
Regenerated axon terminals	3	11
Axon terminals showing "emptiness"	4	21
Axon terminals showing dense material and membranous bodies	2	13
Axon terminals showing marked shrinkage	0	7
Endplates showing marked abnormalities of junctional folds	1	12
Endplate regions showing marked degeneration of Schwann cells and/or their processes	0	22
Proportion of normally structured endplates (%)	85	40

[a] Reprinted with permission from Ref. 72.

week) training revealed a decrease of activities of these enzymes. However, long-term training resulted in relatively higher levels of these enzymes in muscles of mice trained from a young age (21, 73). The above observations supported the concept put forward by Edington and coworkers that for a certain intensity and duration of exercise there is a threshold of age beyond which exercise may be deleterious to the aging animals (74). Similar observations of a threshold of age prevailing for myocardial ATPase and creatine kinase activities were reported by Chesky *et al.* (75). More recent studies by Holloszy and Smith have shown that rats exercised regularly from very young age indeed have had a longer mean life span than their counterpart sedentary controls (76). In addition, studies conducted in the late 1980s and early 1990s have claimed that, even in old age, certain training regimens may have beneficial effects on animals (77) as well as humans (76). Hence, Daw *et al.* have trained Fisher rats from 3 months postpartum to 12 and 27 months. Although with age there was a decrease in the masses of soleus and extensor digitorum longus (EDL) muscles, the trained 27-month-old mice had a significant (113%) increase of soleus muscle mass compared with their sedentary control. No change in EDL muscle weight was observed, and no effect on fiber number was found (77). Very similar results were reported by Brown *et al.*, who observed a considerable hypertrophy of soleus muscle in exercised 27-month-old rats, while running did not prevent atrophy of EDL muscles (78). The conclusion drawn from this last study was that exercise prevented age-related atrophy of weight-bearing soleus and not of the non-weight-bearing EDL muscle. A very interesting recent study by McCormick and Thomas (79) has shown that 10 weeks of treadmill running could induce proliferation of satellite cells in soleus muscles of 26 month old rats. These satellite cells appear to participate in new fiber formation and repair of damaged muscles of the aging rats. Klitgaard *et al.* (34) have exercised old Wistar rats by strength training and swimming. Strength training (rising on the hind limbs) counteracted the effects of age related changes in fiber distribution and muscle atrophy, while swimming did not have any effect. Strength training resulted in elevation of glycogen, phosphocreatine, and ATP contents in the muscles of old trained rats (34). Studies by Ji and coworkers have shown that antioxidant enzyme activities such as superoxide dismutase (SOD) and catalase (Cat) are elevated considerably in striated muscles of aging rats (80–82). An acute bout of exercise (80) and a 10-week treadmill training (81) did not affect the activities of these enzymes (81, 82). Glutathione peroxidase (GPX), on the other hand, was shown to decrease with age and increase after 10 weeks of treadmill running (81). However, in a recent report by Ji (82) all antioxidant enzymes like SOD, GPX, Cat, and glutathione reductase were shown to increase significantly after an exhaustive bout of exercise (83). The above results have led these workers to conclude that both aging and exercise may result in increasing oxidative stress in striated muscles and in other tissues (82).

Several studies on humans have shown that exercise of old people may result in positive adaptation of skeletal muscles. Orlander and Aniasson reported that aerobic types of physical training of 70- to 75-year-old men caused an increase in mitochondrial oxidative capacity, as well as improved anaerobic capacity (83). A study by Frontera *et al.* on untrained healthy human volunteers (ages 60–72 years) demonstrated that strength training could improve the strength of extensors and flexors of knee muscles. In addition, there was a concomitant muscle hypertrophy and increased myofibrillar protein turnover in these elderly people (84). Finally, work by Clarkson and Dedrick has shown that eccentric exercise of the forearm of women over 60 years old caused a similar damage as in young college women. The old women could adapt by repairing the damage as well as young women (85).

Although the above reports may indicate that exercise can be beneficial to sedentary old people, a very recent review by Holloszy (86) has pointed out that from all the available data concerning the effects of exercise on other systems like the respiratory, vascu-

lar, and coronary systems of old people and animals, it is not clear whether strenuous exercise can slow down the aging effects. More research and information are needed to reach such a conclusion (86).

Disuse and Immobilization in Old Age. The question of changes of muscle function with disuse has been discussed extensively by Wilmore (3). Some alterations of muscle structure and function in disuse atrophy are similar, if not identical, to changes that are observed with old age. Musaccia *et al.* (87) in an extensive review of the effects of immobilization on the atrophy of skeletal muscles in animals, have described the major changes that take place following disuse. In general, there is a significant decrease in muscle mass and strength with shifts in fiber types. Some reports have claimed that there were changes in cross sectional area and distributions of type I fibers, while others reported alterations in Type II fibers. Also, immobilization and disuse are followed by rapid inhibition of protein synthesis and a marked increase in protein degradation, usually within several hours after the onset of immobilization. A more recent review by Appell emphasizing human studies (88) has described the major changes that take place in muscles of people. For example, atrophy in humans was followed by much greater atrophy of type I muscle fibers than Type II fibers. Also, in all immobilized muscles, the rate of muscle protein breakdown increased considerably with significant changes in the activity of oxidative enzyme content and loss of mitochondrial function (88). Recently, studies by Carmeli *et al.* (89) on immobilized 25-month-old Wistar rats have shown a marked reduction of 31%–33% in the weights of gastrocnemius and plantaris muscles following 4 weeks of cast immobilization. Also, muscle protein oxidation as measured by protein carbonyl assay increased 4-fold after immobilization. Indeed, studies on protein oxidation of gastrocnemius muscle of young (7-month) and of old (25-month) rats showed a 50% increase in carbonyl content in old muscles (90). Administration of rat growth hormone (GH) to the old animals during the immobilization period attenuated the deleterious effects of immobilization, thus providing a potential means of reducing the degeneration effects of limb immobilization of aged rats (89).

The Effect of Nutrition and Food Restriction. Proper nutrition and food consumption is a major determinant in the well being of humans and animals. The question of whether overfeeding is detrimental and food restriction is beneficial to the health and longevity of humans has been a subject of enormous interest. Dietary restriction (DR) and especially low caloric intake has been shown to extend maximum life span and retard some aging processes in rodents (91). However, the effects of nutrition and DR on the aging muscle are not clear. DeLuise and Harber examined the effect of sucrose overfeeding on the soleus muscles of young and old mice. In both age groups, there was a parallel increase of the oxygen consumption and Na^+K^+ pump activity of the soleus of the overfed sucrose animals (92). On the other hand, old rats that were food restricted to keep their body weights low had significantly higher rates of muscle glucose uptake than their sedentary freely eating controls (38). The above studies demonstrated that muscles of aged animals can respond metabolically quite well to high and low intake of calories.

Studies by McCarter and McGee on Fisher rats of different ages, fed with various calorie-restricted diets, could not detect any functional or compositional changes with age or diets in the soleus and lateral omohyoidous muscles (58). Somewhat later studies by Borehamm *et al.* on soleus and extensor digitorum longus (EDL) muscles of rats from weaning to old age have shown some important effects of long-term dietary restriction. For example, the blood capillary/fiber ratio was considerably lower in the muscles of dietary restricted animals. Also, the increase with age of muscle connective tissue was curtailed by about 50% in the DR rats. Thus, the conclusion reached by the above workers was that age associated pathological changes could be delayed or slowed down in muscles of DR old animals (94).

Aged Muscles Affected by Diseases, Drugs, and Injuries. A good number of elderly people in our society, unfortunately, suffer from what have been called the diseases of old age. Diseases of the skeleton and joints, like osteoporosis and arthritis; diseases of the brain and CNS, like strokes, Alzheimer's disease, and Parkinson's disease; and myopathies, which resemble muscular dystrophy, are all examples of these "old age" diseases, which can contribute to muscle degeneration and weakness. In many of these maladies, muscle atrophy and dysfunction are due to reduced control and stimuli of the neural motor system (95). In addition, extended exposure of older people and animals to drugs, like steroids and other anabolic hormones (growth hormone, insulin, thyroid hormones), has been shown to affect their muscles (95).

Alcohol also has its adverse effects on skeletal muscles. Indeed, alcoholic myopathies have been described in people drinking large quantities of alcohol (96, 97) with a typical Type II fiber atrophy observed and general fiber degeneration and muscle weakness.

Intense eccentric exercise can cause damage and injury to skeletal muscles of humans (98) and rats (99). In an interesting study by Brooks and Faulkner (100), EDL muscles of young and old mice were subjected to the same contraction-induced injury using lengthening contraction. Injury was assessed by counting fiber number and measurements of maximum tetanic force which experimentally was adjusted to be the same for

both age groups. The capacity for recovery from injury was evaluated in the following weeks after the onset of the injury. By 28 days, muscles of young mice recovered completely, while injured muscles of old mice were 84% to 87% of the control values using the above parameters as criteria. These studies demonstrated that the capacity of muscles of old animals to recover from injury is decreased compared with young animals. In a parallel study, in an attempt to ascertain the involvement of oxygen free radicals in muscle injury, the above workers treated mice of various ages with the antioxidant enzyme polyethylene glycol superoxide dismutase (PEG-SOD). The PEG-SOD-treated animals had better recovery values than the nontreated controls in all age groups. But, the old animals recovered less well from the free radical induced injury (101). These results also showed that, in addition to the initial mechanical damage caused by injury, oxidant-chemical damage may contribute to muscle injury.

Conclusions

With age, people and animals tend to become less mobile. Therefore, some of the observed changes in muscles as a function of age can be due to disuse atrophy and not necessarily due to the intrinsic aging processes. Nevertheless, the decrease in skeletal muscle performance with age is an important phenomenon which has a direct effect on elderly human beings. Understanding the relative contributions and the complex mechanisms by which intrinsic and extrinsic factors influence the functionality of muscles of old age is an essential step toward devising ways to ameliorate the age-related decline in muscle function. Adequate training and exercise have been shown to provide one such promising means as older animals and humans could adapt quite well to certain exercise regimes. However, other treatments, like administration of anabolic hormones (i.e., growth hormone) and provision of antioxidants like vitamin E, may also prove beneficial.

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