brief review

Skeletal muscle weakness in old age: underlying mechanisms

SUSAN V. BROOKS and JOHN A. FAULKNER

Institute of Gerontology and Department of Physiology, University of Michigan, Ann Arbor, MI 48109-2007

ABSTRACT

BROOKS, S. V. and J. A. FAULKNER. Skeletal muscle weakness in old age: underlying mechanisms. *Med. Sci. Sports Exerc.* Vol. 26, No. 4, pp. 432–439, 1994. Maintenance of muscle mass and strength contributes to mobility which impacts on quality of life. Although muscle atrophy, declining strength, and physical frailty are generally accepted as inevitable concomitants of aging, the causes are unknown. Clarification of the mechanisms responsible for these changes would enhance our understanding of the degree to which they are preventable or treatable. The decline in muscle function between maturity and old age is similar for muscles of many different animals including human beings, and is typified by the decreases of ~35% in maximum force, ~30% in maximum power, and 20% in normalized force ($kN \cdot m^{-2}$) and power ($W \cdot kg^{-1}$) of extensor digitorum longus (EDL) muscles in old compared with adult mice. Much of the age-associated muscle atrophy and declining strength may be explained by motor unit remodeling which appears to occur by selective denervation of muscle fibers with reinnervation by axonal sprouting from an adjacent innervated unit. Muscles in old mice appear more susceptible to injury than muscles in young or adult mice and have a decreased capacity for recovery. The process of age-related denervation may be aggravated by an increased susceptibility of muscles in old animals to contraction-induced injury coupled with impaired capacity for regeneration.

AGING, FRAILTY, STRENGTH, HUMAN BEINGS, RATS, MICE

All body movements are produced by contractions of skeletal muscles. Consequently, any impairment in the functional properties of skeletal muscle results in some degree of immobility. A loss of mobility inhibits participation in physical activities, as well as successful performance of the necessary activities of daily living. In addition, it is estimated that one-third to one-half of people over 65 yr of age experience at least one fall per year (9,55) and many of these falls contribute significantly to morbidity and mortality (52). While a cause-effect relationship between muscle strength and incidence of falling has not been established, correlative studies support this hypothesis (43,52,55,58). Compared with age-matched control subjects, elderly nursing home residents with a history of frequent falls showed significantly lower values for strength and power of the four muscle groups associated with balance: the knee flexors and extensors, and ankle plantar, and dorsiflexors (58).

Physical frailty describes the summation of the effects of muscle atrophy, declining muscle strength and power, fatigue, and injury (21). Although increasing physical frailty is widely accepted as an inevitable concomitant of old age, the underlying causes are not known. Consequently, the degree to which these changes are preventable and treatable is not clear. In addition, while the decreases in muscle mass, strength, and power may be related to decreased activity levels throughout the lifetime, maintenance of physical activity does not appear to protect skeletal muscles completely from these age-related decrements. Even superbly trained world class athletes, who at any given age display higher values for maximum and sustained strength and power than untrained individuals, show similar trends and time courses of decline in structural and functional properties (48,53,54).

The structural and functional deficits are reflected in decreased performance by these athletes and are typified by the world records for the 200-m sprint by individuals of different ages (Fig. 1) (48). The mean ages for peak performances in other sports, such as swimming, tennis, baseball, and golf, range from the late teens to only the early thirties (53). These data on highly trained individuals are not confounded by intervening variables such as debilitating diseases or physical inactivity. Interestingly, while the strength data in Figure 1 were obtained from untrained individuals, the decrease in the level of performance in the 200-m sprint superimposes the relationship of the decrease in leg strength when both variables are expressed as a percentage of their respective maximum values. These observations suggest that age-related deficits, which are largely inevitable and independent of de-

0195-9131/94/2604-0432$3.00/0
MEDICINE AND SCIENCE IN SPORTS AND EXERCISE

Submitted for publication February 1993.
Accepted for publication July 1993.

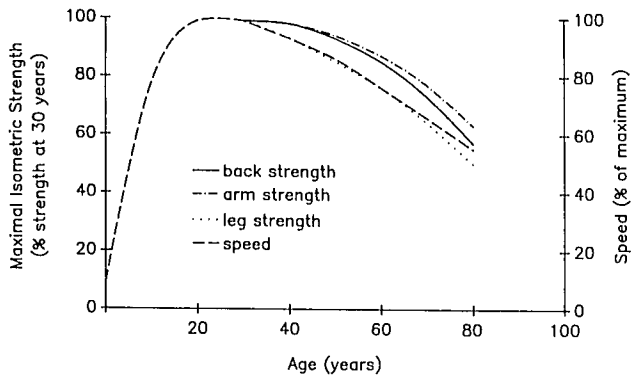

Figure 1—Data from a cross-sectional study of maximum isometric strength of three muscle groups in human beings of different ages are plotted along with the world records for average running speeds of the men's 200-m sprint for men of different ages. (Reproduced from Asmussen, E. Aging and exercise. In: *Environmental Physiology: Aging, Heat and Altitude*, sec. III, S. M. Horvath and M. K. Yousef (Eds.). New York: Elsevier North Holland, Inc., 1980, pp. 419–428; and Moore II, D. H. A study of age group track and field records to relate age and running speed. *Nature* 253:264–265, 1975, with permission.) Strength data are expressed as percentages of the strength measured for 30-yr-olds and speed data are presented as percentages of the maximum value. Note the curve for leg strength and speed almost superimpose.

creases in physical activity, occur in the skeletal muscles of animals, including human beings. This review will address each of the components of physical frailty and discuss the possible mechanisms of the largely irreversible changes associated with aging.

MUSCLE ATROPHY

By 60–70 yr of age, muscle mass of human beings decreases by 25–30% (29) and in mice and rats by 10–25% (4,25,31,38). Superficially, the decrease in muscle mass that is observed with aging appears to be analogous to the atrophy associated with a decrease in physical activity (for review see ref. 24). With a decrease in physical activity, such as occurs following the casting of a limb or with bed rest, the muscle atrophy results from a decrease in the cross-sectional area (CSA) of individual fibers and no decrease in the total number of fibers. For muscles in young and adult animals, muscle atrophy is reversible and muscle mass and CSA are restored when normal activity levels resume (45). In contrast, the muscle atrophy that occurs in old age appears to involve some loss of muscle fibers (29,42), and, therefore, is not completely reversible.

Complete fiber counts in mice and rats indicate that fiber number is highly conserved throughout the lifetime of these rodents, decreasing by at most 5% in old age (15,59). Some indirect evidence supports the premise that the muscles of human beings, unlike those of rodents, may lose fibers throughout the life span. The difficulty is that at any age the muscles of human beings contain hundreds of thousands of fibers; consequently, direct fiber counts are not feasible. Estimates of fiber number have been made using whole muscle cross-sections from cadavers or indirect measurements of muscle CSA by computerized tomography of subjects and mean single fiber areas from biopsy samples (29). The total number of fibers is estimated by dividing the whole muscle CSA by the mean single fiber CSA. The data provided by this technique support the concept that the number of fibers in human muscles decreases continuously throughout the life span: 23% between birth and young adulthood, and an additional 24% between adulthood and old age (29). From muscles of cadavers, total fiber number has also been estimated as the product of the total muscle CSA (mm^2) and the mean number of fibers per mm^2 (42). The data obtained using this technique suggest that fiber number reaches a maximum at approximately 25 yr of age and decreases by ~40% by age 80 (42). The latter results indicate that the loss in fiber number early in life may be artifactual, due to errors in the technique used to make the estimate (29,42).

Prior to 60–70 yr of age, little change in the single fiber CSA of any of the three fiber types is observed (30). In spite of this observation, a shift in the proportions of Type I and Type II muscle fibers may actually contribute to muscle atrophy. Type II fibers tend to be large, while in general Type I fibers are small in CSA. A decrease in the number of large Type II fibers with an accompanying increase in the number of small Type I fibers could decrease the total muscle fiber CSA and decrease muscle mass, yet no differences would be observed in the single fiber CSA of any of the three fiber types.

In age groups older than 70 yr, the mean area of Type II fibers decreases by 15–20% (30) and the percentage of Type II fibers decreases by as much as 40% (37). In fact, elderly patients who are bedridden often display only two fiber types, Type I and Type IIB, with complete loss of all Type IIA fibers. The decrease in the proportion of Type II fibers could be the result of either the conversion of Type II fibers to Type I fibers, or a direct loss in the total number of Type II fibers.

ABSOLUTE FORCE

Over 150 yr ago, Quetelet (50) made the original observations of impaired skeletal muscle function with age. During the ensuing years, studies of many different muscles and muscle groups led to the overall conclusion that, between 30 and 80 yr of age, muscle strength decreases 30–40% (Fig. 1) (2,39,60,61). The decrease in strength correlates well with the decrease in muscle mass. Based on this equivalency of the decreased strength and decreased mass, Grimby and Saltin (29) concluded that there was no reason to postulate any intrinsic qualitative changes in skeletal muscle or muscle fibers with aging. This conclusion was based on indirect evidence and the hypothesis that the loss in strength with

aging is fully explained by muscle atrophy is difficult to test rigorously in human beings.

The changes in functional properties of skeletal muscles with age may be studied more accurately through measurements of whole skeletal muscles of young (2–3 months), adult (9–12 months), and old (24–28 months) rats and mice. Experiments are performed *in vitro* using supramaximal electrical stimulation. As with human beings, a decrease in maximum isometric tetanic force of 20–35% has been reported for muscles of old compared with adult mice (4,49) and rats (11,31,38), with similar deficits for both slow and fast muscles (4,49). Although the deficit in force for the muscles of rodents is less than the deficit in strength reported for elderly human beings, the data support the idea that a decrease in maximum force development with age is not unique to human beings.

SPECIFIC FORCE

The force developing capacity of skeletal muscles is proportional to total muscle fiber CSA. Therefore, accurate estimations of the total fiber CSA are necessary to determine the force per unit area or specific force ($kN \cdot m^{-2}$). An accurate measure of the specific force is essential for the comparison of the intrinsic force generating capabilities of muscle fibers, muscles, or groups of muscles from individuals of different ages. In this paper, weakness is defined as the characteristic of a muscle fiber, motor unit, whole muscle, or group of muscles that produces less specific force than expected (21). Muscles may be relatively small, or atrophied, and still have a normal maximum specific force and, consequently, would not be termed "weak."

Accurate measurements of total muscle fiber CSA in human beings are not possible because direct measurements of the muscle mass and the length of fibers cannot be made. Estimates of the total fiber CSA of groups of muscles involved in the contractions depend on indirect measurements by computerized tomography which would be accurate only for a completely parallel fibered muscle. Some estimates of maximum specific strength of human beings suggest that atrophy alone does not explain the decrease in voluntary strength with age (8,14,57,61) and muscles from elderly subjects are in fact weaker than those of young subjects. In contrast, others have found no difference in maximum strength normalized for whole muscle CSA (28). The different results may arise from the architectural complexity of the muscle groups involved.

For isolated whole muscles of rodents, accurate measurements of both muscle mass and fiber length permit valid estimations of total muscle fiber CSA. When the maximum isometric force observed for the muscles of old mice (4,49) and rats (25,31,38) is normalized by the smaller total muscle fiber CSA, a deficit of ~20% in specific isometric force remains unexplained by atrophy (4,11,49).

Although the magnitudes of the deficits in maximum specific isometric force observed for muscles from human beings and rodents are similar, the mechanisms responsible for the deficit may be quite different. In muscle groups of human beings, a change in the complex architecture of muscle with aging could account for some part of the decrease in specific strength (46,61), but definitive studies have not been possible. In contrast, in single muscles of mice, changes with age in extracellular components are not a major factor and changes in architecture or water content do not occur (4). Although the concentration of connective tissue in skeletal muscle does increase with age (1), the magnitude of the increase is not sufficient to affect significantly the amount of noncontractile tissue in the cross-section. Consequently, connective tissue content has little impact on the estimation of specific force. Based on the totality of these observations, the most defensible working hypothesis is that for whole muscles of mammals, the site of the deficit in specific isometric force must be located in single fibers and is confined to a decrease in the number of cross-bridges per unit area, or a decrease in the average force developed per cross-bridge (4,49).

FORCE-VELOCITY RELATIONSHIPS

In addition to isometric contractions, skeletal muscles may shorten or be lengthened during contractions (24). Following activation, the type of contraction that occurs depends on the interaction between the force developed by the muscle and the load placed on the muscle. When the load is fixed or immovable, an isometric contraction occurs. If the force developed by the muscle is greater than the load on the muscle, the muscle will shorten during the contraction, while a load that is greater than the force developed by the muscle will result in a lengthening contraction.

The force-shortening velocity relationship is hyperbolic, intersecting the force and velocity axes at maximum isometric force and maximum velocity of shortening (V_{max}), respectively. The curvature of the relationship is dependent on the fiber type composition of the muscle, with slow muscles showing greater curvature than fast (23,51). The effect of age on the velocity of shortening of human muscles has not been studied extensively (29,39). For the limb muscles of mice and rats, V_{max} of both slow and fast muscles does not appear to change, even in very old animals (4,25,49). In addition, when both force and velocity are normalized to the maximum value, the curvature of the relationships is not different for either slow or fast muscles of old compared with young animals. The stability with aging of the entire force-shortening velocity relationship, including V_{max}, is consistent with histochemical (18,19,26,38) and biochemical (26) character-

istics of slow soleus and fast extensor digitorum longus (EDL) muscles. The data support the hypothesis that, throughout the life span of small rodents, no change occurs in the myosin isoform composition of skeletal muscles composed exclusively of one type of fiber.

Age-associated alterations were observed in the force-velocity relationships of diaphragm strips from hamsters (63). The V_{max}, as well as the velocity of shortening at given relative afterloads decreased for the diaphragm strips from the old compared with the young and adult animals. A decrease in velocity of shortening of the diaphragm muscle with aging may be an indication that with aging skeletal muscles that are composed of heterogeneous fiber types do not maintain the same myosin composition.

During lengthening contractions, force increases with velocity to a level approximately two times maximum force (36), but further increases in velocity do not result in higher forces (34,36,44). Compared with isometric contractions, the number of attached cross-bridges increases by only ~10% during lengthening contractions (34,44). Consequently, the predominant factor in the increased active force during lengthening appears to be an increased force developed per cross-bridge due to increased cross-bridge strain (44).

Soleus muscles of old mice show significant deficits in specific force during isometric and shortening contractions, but the specific forces developed during lengthening contractions were not different for muscles of old and young mice (49). Phillips and her associates (49) conclude from this observation that the decrease in maximum isometric specific force is not due to a decreased number of cross-bridges in the cross-section or an inability to activate them. The report that muscle strength of both the knee flexors and extensors in elderly women was much less affected by age during lengthening than shortening contractions (56) is consistent with the observations on mouse muscles (49).

MAXIMUM AND SUSTAINED POWER OUTPUT

Since most everyday tasks require movement, the ability of muscles to generate and sustain power is of great consequence. The power output of a muscle is the product of the velocity of shortening and the average force developed by the muscle. When EDL muscles from young, adult, and old mice were compared for the ability to generate power, the maximum power (W) developed by muscles of old mice was ~30% lower than that of muscles of adult mice (6). Like the age-related deficit in force, ~10% of the deficit in power output could be explained by atrophy, but a 20% deficit in normalized power ($W \cdot kg^{-1}$) remained (6). The primary cause of the deficit in power was the 20% deficit in specific force.

Brooks and Faulkner (6) have proposed that the fatigability of a muscle is better assessed by the ability of the muscle to sustain force or power, rather than by the decrement in force or power observed over time. The graded exercise test for physical work capacity has provided a valid measure of the fatigue resistance of the total organism (3), and similarly, the ability of a muscle to sustain force or power during repeated contractions provides a valid measure of the fatigue resistance of a muscle. This type of progressive exercise test initiates contractions at low energy requirement or power and then gradually increases the intensity to the maximum level that can be sustained. The intensity is increased by increasing the fraction of the work-rest cycle during which work is done. This duty cycle can be increased by increasing either the duration of the contractions or the frequency with which they occur (6).

The ability of muscles from young, adult, and old mice to sustain power has been measured *in situ* during repeated shortening contractions with steadily increasing duty cycles (6). The maximum sustained powers ($W \cdot kg^{-1}$) of muscles of adult and old mice were 55% and 45%, respectively, of the value for muscles from young mice (Fig. 2). In addition, the muscles of adult and old mice were not able to maintain the duty cycles for repeated contractions achieved by the young mice (Fig. 2). Sustained power requires a balance between the rate of energy use and rate of energy production (17). Both the delivery of oxygen to muscles through decreased blood flow (32) and decreased capacity for oxidative metabolism (13,20) provide possible limitations to the ability of the muscles of adult and old mammals to maintain energy balance (17). The metabolic limitations appear to arise by 12 months of age in these mice and become increasingly more severe with aging (6).

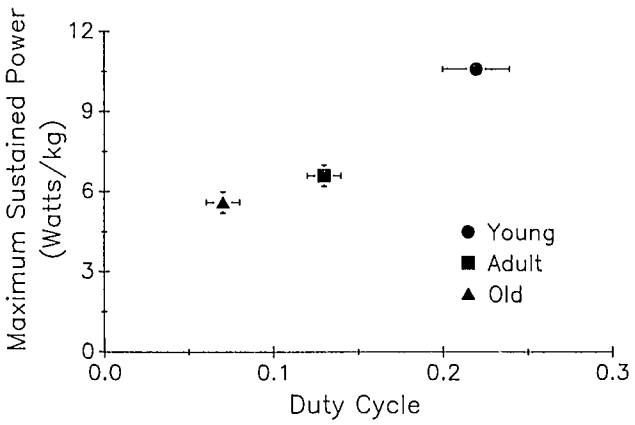

Figure 2—The relationship for young, adult, and old mice between the maximum power that could be sustained for 30 min and the duty cycle at maximum sustained power. Values are means ± SEM (reproduced from Faulkner, J. A., S. V. Brooks, and E. Zerba. Skeletal muscle weakness, fatigue, and injury: inevitable concomitants of aging? *Hermes* 21:269–280, 1990, with permission).

CONTRACTION-INDUCED INJURY

Skeletal muscles can be injured by their own contractions during everyday activities, particularly during activities with a predominance of lengthening contractions (47). When muscles of young, adult, and old mice were administered the same protocol of lengthening contractions, the amount of injury to muscle fibers in the muscles of old mice was significantly greater than that observed for the muscles of young or adult mice (Fig. 3) (62). In addition, when muscles from young and old mice were injured to the same degree, the muscle fibers in the muscles of old animals recovered less well (Fig. 3) (5). While the muscles in young and adult mice recovered fully from contraction-induced injury within a couple of weeks, the muscles of old mice did not recover completely even after 2 months (5).

Muscles in old animals also show a decreased regenerative capacity following free whole muscle transplantation (11). Under these circumstances, the whole muscle degenerates as a result of the ischemic injury. The recovery of mass and maximum force of grafts following transplantation in young rats was 2.5 times greater than in old rats. Interestingly, the results were the same regardless of the age of the donor. Muscles from young or old rats transplanted into young rats regenerated equally well while muscles from young or old rats transplanted into old rats regenerated equally poorly (12). Apparently, the inherent regenerative capacity of the muscles in old animals is not decreased, but the host environment is not suitable for successful regeneration. Impaired ability for reinnervation in the old host is a contributing factor to the decrease in muscle regenerative capacity (11). Other possibilities include impaired revascularization, hormonal influences, nutrition, pathology, or macrophage function.

The prolonged deficits that are observed in the muscles of old mice following degeneration and regeneration resemble those that arise normally in the muscles of old mice. Since various magnitudes of injury are likely occurring throughout the life span of an animal, an increased susceptibility to contraction-induced injury coupled with a decreased ability to recover from injury may well give rise to both muscle atrophy and muscle weakness in old animals.

MOTOR UNIT REMODELING

Much of the age-associated muscle atrophy and declining strength may be explained by motor unit remodeling. Motor unit remodeling occurs as a consequence of the natural cycle of turnover of the synaptic connections which occurs at the neuromuscular junction, by the processes of denervation, axonal sprouting, and reinnervation (7). While grouping of Type I fibers is common in muscles of the elderly, abnormalities suggestive of histopathological changes are relatively rare (30,33,41). The assumption is that grouping of Type I fibers results from the denervation of Type II fibers with reinnervation by axonal sprouting from Type I fibers from an adjacent innervated unit (7,10). Presumably, Type II fibers that are not reinnervated undergo denervation atrophy (29). In addition, indirect estimates indicate a decrease in the total number of motor units (Fig. 4) and an increase in the size of the remaining motor units in the muscles of elderly human beings (10).

In muscles with heterogeneous fiber types, data are consistent with the occurrence of similar processes of

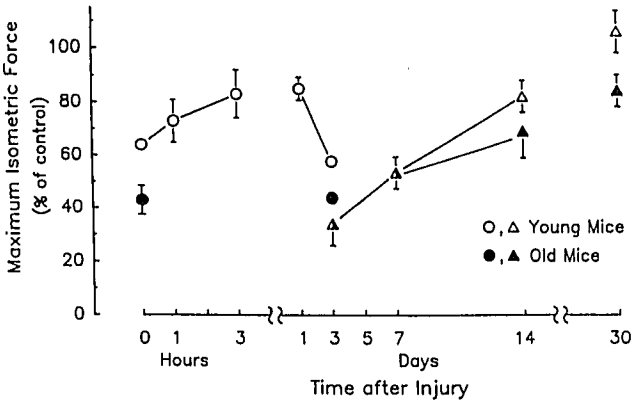

Figure 3—Maximum isometric force of extensor digitorum longus muscles from young (*open symbols*) and old (*filled symbols*) mice at selected times after lengthening contractions. Values are expressed as a percentage of the maximum force of the uninjured control muscle. *Circles* and *triangles* represent lengthening contraction protocols of different duration (reproduced from Faulkner, J. A., S. V. Brooks, and E. Zerba. Skeletal muscle weakness and fatigue in old age: underlying mechanisms. In: *Annual Review of Gerontology and Geriatrics*, V. J. Cristofalo and M. P. Lawton (Eds.). New York: Springer, 1991, pp. 147–166, with permission).

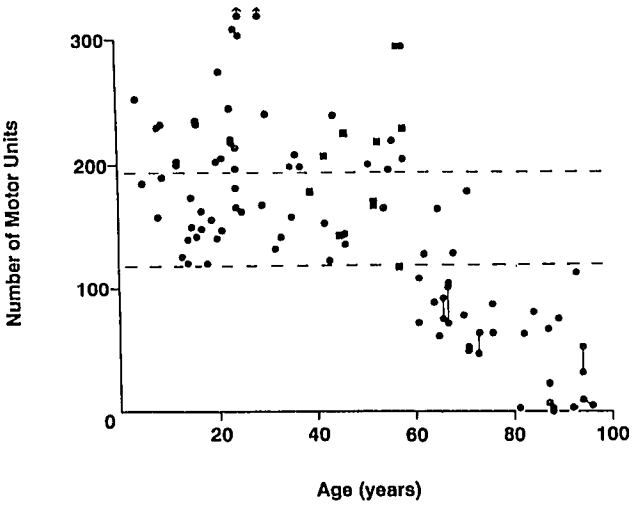

Figure 4—The number of functional motor units in the extensor digitorum brevis muscle for individuals of different ages (reproduced from Campbell, M. J., A. J. McComas, and F. Petito. Physiological changes in ageing muscles. *J. Neurol. Neurosurg. Psychiatry* 36:74–182, 1973, with permission).

motor unit remodeling in old rats (19,35). For medial gastrocnemius muscles of 27-month-old rats, the mean maximum force of Type II motor units was 70% that of comparable motor units in 12-month-old rats, while that of Type I motor units was 250% of the adult value (35). In addition, the total number of motor units in both soleus (19) and medial gastrocnemius (35) muscles of rats decreased by ~30% and the size of the remaining slow motor units increased. Both the mean number of muscle fibers in a motor unit, as well as the mean total area of the fibers in a motor unit increased.

Motor unit remodeling in aging rats appears to occur by selective denervation of Type II fibers with reinnervation by collateral sprouting of nerves from fibers in the Type I motor units. An alternate interpretation is that denervation of both Type I and Type II fibers occurs but that Type I motoneurons are more efficient at reinnervation of muscle fibers (16). The greater efficiency might result from faster axonal growth (40) or superiority in establishing permanent connections with muscle fibers (27).

The concept of selective denervation of fast fibers and reinnervation by sprouting of motor nerves from slow fibers does not contradict the histochemical (18), biochemical (26), or physiological (4,49) observations that suggest that no changes occur throughout the life span in the myosin composition of the soleus and EDL muscles of rodents (22). The soleus and EDL muscles of these rodents are very homogeneous with respect to fiber type and denervation of faster fibers would not produce changes in the proportions of fiber types, the myosin ATPase activity, or the normalized force-shortening velocity relationship that could be identified experimentally. In contrast, most of the muscles in human beings have approximately equal proportions of slow and fast fibers (23). With aging, if motor nerves of fast motor units are more likely to degenerate than those of slow motor units, human muscles would show a greater change in fiber type composition, velocity and power than rodents. The 75% decrease in motor unit number reported for some human muscles (10) compared with the 30% decrease in rat muscles (19,35) suggests that muscles in human beings may be more susceptible than those of rodents to the phenomenon of age-related denervation atrophy.

SUMMARY

The phenomena of impaired capacities for the development of maximum and sustained strength and power of muscles of human beings appear to begin shortly after the age of 30. The decline progresses slowly at first and then more rapidly after age 65–70. A promising hypothesis for irreversible age-related changes in skeletal muscles is that specific morphological aspects of faster motor nerves result in the preferential degeneration of these nerves and the denervation of the faster muscle fibers (35). The process of selective denervation, atrophy, and degeneration of motor nerves to muscle fibers in old animals may explain the Type II fiber atrophy (30), the loss in the number of fibers (15), and the decrease in muscle mass (4,29). The reinnervation of some denervated fibers by sprouting of motor nerves may account for the clustering of fibers types in muscles of old rodents (35), and human beings (29,41), as well as the increase in the size of slow motor units (35). The process of age-related denervation atrophy may be aggravated by an increased susceptibility of muscles in old animals to contraction-induced injury (62) and by the impaired capacity for regeneration (5,11,12).

This review is based on a tutorial lecture given by John A. Faulkner at the 1992 Annual Meeting of the American College of Sports Medicine. We thank Richard Hinkle for his help in the preparation of this manuscript. The research was supported in part by grants from the United States Public Health Service, National Institute on Aging: AG06157 and AG00114. The latter provided fellowship support to Susan V. Brooks.

Address for correspondence: John A. Faulkner, Institute of Gerontology and Department of Physiology, University of Michigan, Ann Arbor, MI 48109-2007.

REFERENCES

1. ALNAQEEB, M. A., N. S. AL ZAID, and G. GOLDSPINK. Connective tissue changes and physical properties of developing and ageing skeletal muscle. *J. Anat.* 139:677–689, 1984.
2. ASMUSSEN, E. Aging and exercise. In: *Environmental Physiology: Aging, Heat and Altitude*, sec. III, S. M. Horvath and M. K. Yousef (Eds.). New York: Elsevier North Holland, Inc., 1980, pp. 419–428.
3. ÅSTRAND, I. Aerobic work capacity in men and women with special reference to age. *Acta Physiol. Scand. Suppl.* 169:1–92, 1960.
4. BROOKS, S. V. and J. A. FAULKNER. Contractile properties of skeletal muscles from young, adult, and aged mice. *J. Physiol. (Lond.)* 404:71–82, 1988.
5. BROOKS, S. V. and J. A. FAULKNER. Contraction-induced injury: recovery of skeletal muscles in young and old mice. *Am. J. Physiol.* 258:C436–C442, 1990.
6. BROOKS, S. V. and J. A. FAULKNER. Maximum and sustained power of extensor digitorum longus muscles from young, adult, and old mice. *J. Gerontol.* 46:B28–B33, 1991.
7. BROWN, M. C., R. L. HOLLAND, and W. G. HOPKINS. Motor nerve sprouting. *Annu. Rev. Neurosci.* 4:17–42, 1981.
8. BRUCE, S. A., D. NEWTON, and R. C. WOLEDGE. Effect of age on voluntary force and cross-sectional area of human adductor pollicis muscle. *Q. J. Exp. Physiol.* 74:359–362, 1989.
9. CAMPBELL, A. J., J. REINKEN, B. C. ALLAN, and G. S. MARTINEZ. Falls in old age: a study of frequency and related clinical factors. *Age Ageing* 10:264–270, 1981.
10. CAMPBELL, M. J., A. J. MCCOMAS, and F. PETITO. Physiological changes in ageing muscles. *J. Neurol. Neurosurg. Psychiatry* 36: 74–182, 1973.
11. CARLSON, B. M. and J. A. FAULKNER. Reinnervation of long-term denervated rat muscle freely grafted into an innervated limb. *Exp. Neurol.* 102:50–56, 1988.
12. CARLSON, B. M. and J. A. FAULKNER. Muscle transplantation between young and old rats: age of host determines recovery. *Am. J. Physiol.* 256:C1262–C1266, 1989.
13. CARTEE, G. D. and R. P. FARRAR. Muscle respiratory capacity and

$\dot{V}O_{2max}$ in identically trained young and old rats. *J. Appl. Physiol.* 63:257–261, 1987.
14. DAVIES, C. T. M., D. O. THOMAS, and M. J. WHITE. Mechanical properties of young and elderly human muscle. *Acta Med. Scand. Suppl.* 711:219–226, 1986.
15. DAW, C. K., J. W STARNES, and T. P. WHITE. Muscle atrophy and hypoplasia with aging: impact of training and food restriction. *J. Appl. Physiol.* 64:2428–2432, 1988.
16. DESYPRIS, G. and D. J. PARRY. Relative efficacy of slow and fast α-motoneurons to reinnervate mouse soleus muscle. *Am. J. Physiol.* 258:C62–C70, 1990.
17. DUDLEY, G. A. and S. J. FLECK. Metabolite changes in aged muscle during stimulation. *J. Gerontol.* 39:183–186, 1984.
18. EDDINGER, T. J., R. L. MOSS, and R. G. CASSENS. Fiber number and type composition in extensor digitorum longus, soleus, and diaphragm muscles with aging in Fisher 344 rats. *J. Histochem. Cytochem.* 33:1033–1041, 1985.
19. EDSTRÖM, L. and L. LARSSON. Effects of age on contractile and enzyme-histochemical properties of fast- and slow-twitch single motor units in the rat. *J. Physiol. (Lond.)* 392:129–145, 1987.
20. FARRAR, R. P., T. P. MARTIN, and C. M. ARDIES. The interaction of aging and endurance exercise upon the mitochondrial function of skeletal muscle. *J. Gerontol.* 36:642–647, 1981.
21. FAULKNER, J. A., S. V. BROOKS, and E. ZERBA. Skeletal muscle weakness, fatigue, and injury: inevitable concomitants of aging? *Hermes* 21:269–280, 1990.
22. FAULKNER, J. A., S. V. BROOKS, and E. ZERBA. Skeletal muscle weakness and fatigue in old age: underlying mechanisms. In: *Annual Review of Gerontology and Geriatrics*, V. J. Cristofalo and M. P. Lawton (Eds.). New York: Springer, 1991, pp. 147–166.
23. FAULKNER, J. A., D. R. CLAFLIN, and K. K. MCCULLY. Power output of fast and slow fibers from human skeletal muscles. In: *Human Power Output*, N. L. Jones, M. McCartney, and J. McComas (Eds.). Champaign, IL: Human Kinetics Publishers, 1986, pp. 81–91.
24. FAULKNER, J. A., H. J. GREEN, and T. P. WHITE. Response and adaptation of skeletal muscle to changes in physical activity. In: *Physical Activity, Fitness and Health*, C. Bouchard (Ed.). Champaign, IL: Human Kinetics Publishers, 1994, pp. 343–357.
25. FITTS, R. H., J. P. TROUP, F. A. WITZMANN, and J. O. HOLLOSZY. The effect of ageing and exercise on skeletal muscle function. *Mech. Ageing Dev.* 27:161–172, 1984.
26. FLORINI, J. R. and D. Z. EWTON. Skeletal muscle fiber types and myosin ATPase activity do not change with age or growth hormone administration. *J. Gerontol.* 44:B110–B117, 1989.
27. FOEHRING, R. C., G. W. SYPERT, and J. B. MUNSON. Motor unit properties following cross-reinnervation of cat lateral gastrocnemius and soleus muscles with medial gastrocnemius nerve. I. Influence of motoneurons on muscle. *J. Neurophysiol.* 57:1210–1226, 1987.
28. FRONTERA, W. R., V. A. HUGHES, K. J. LUTZ, and W. J. EVANS. A cross-sectional study of muscle strength and mass in 45- to 78-yr-old men and women. *J. Appl. Physiol.* 71:644–650, 1991.
29. GRIMBY, G. and B. SALTIN. The aging muscle. *Clin. Physiol.* 3:209–218, 1983.
30. GRIMBY, G., B. DANNESKIOLD-SAMSOE, K. HVID, and B. SALTIN. Morphology and enzymatic capacity in arm and leg muscles in 78–82 year old men and women. *Acta Phys. Scand.* 115:124–134, 1982.
31. GUTMANN, E. and B. M. CARLSON. Regeneration and transplantation of muscles in old rats and between young and old rats. *Life Sci.* 18:109–114, 1976.
32. IRION, G. L., U. S. VASTHARE, and R. F. TUMA. Age-related change in skeletal muscle blood flow in the rat. *J. Gerontol.* 42:660–665, 1987.
33. JENNEKENS, F. G. I., B. E. TOMLINSON, and J. N. WALTON. Histochemical aspects of five limb muscles in old age: an autopsy study. *J. Neurol. Sci.* 14:259–276, 1971.
34. JULIAN, F. J. and D. L. MORGAN. The effect on tension of non-uniform distribution of length changes applied to frog muscle fibres. *J. Physiol. (Lond.)* 293:379–392, 1979.
35. KANDA, K. and K. HASHIZUME. Changes in properties of the medial gastrocnemius motor units in aging. *J. Neurophysiol.* 61: 737–746, 1989.
36. KATZ, B. The relation between force and speed in muscular contraction. *J. Physiol. (Lond.)* 96:45–64, 1939.
37. LARSSON, L. Histochemical characteristics of human skeletal muscle during aging. *Acta Phys. Scand.* 117:469–471, 1983.
38. LARSSON L. and L. EDSTRÖM. Effects of age on enzyme-histochemical fibre spectra and contractile properties of fast- and slow-twitch skeletal muscles in the rat. *J. Neurol. Sci.* 76:69–89, 1986.
39. LARSSON, L., G. GRIMBY, and J. KARLSSON. Muscle strength and speed of movement in relation to age and muscle morphology. *J. Appl. Physiol.* 46:451–456, 1979.
40. LEWIS, D. M., A. ROWLERSON, and S. N. WEBB. Motor units and immunohistochemistry of cat soleus muscle after long periods of cross-reinnervation. *J. Physiol. (Lond.)* 325:403–418, 1982.
41. LEXELL, J., D. DOWNHAM, and M. SJÖSTRÖM. Distribution of different fiber types in human skeletal muscles: fibre type arrangement in m. vastus lateralis from three groups of healthy men between 15 and 83 years. *J. Neurol. Sci.* 72:211–222, 1986.
42. LEXELL, J., C. C. TAYLOR, and M. SJÖSTRÖM. What is the cause of the ageing atrophy? Total number, size and proportion of different fiber types studied in whole vastus lateralis muscle from 15- to 83-year-old men. *J. Neurol. Sci.* 84:275–294, 1988.
43. LIPSITZ, L. A., P. V. JONSSON, M. M. KELLEY, and J. S. KOESTNER. Causes and correlates of recurrent falls in ambulatory frail elderly. *J. Gerontol.* 46:M114-M122:1991.
44. LOMBARDI, V. and G. PIAZZESI. The contractile response during steady lengthening of stimulated frog muscle fibres. *J. Physiol. (Lond.)* 431:141–171, 1990.
45. MACDOUGALL, J. D., G. C. B. ELDER, D. G. SALE, J. R. MOROZ, and J. R. SUTTON. Effects of strength training and immobilization on human muscle fibers. *Eur. J. Appl. Physiol.* 43:25–34, 1980.
46. MAUGHAN, R. J., J. S. WATSON, and J. WEHR. Strength and cross-sectional area of human skeletal muscle. *J. Physiol. (Lond.)* 338: 37–49, 1983.
47. MCCULLY, K. K. and J. A. FAULKNER. Injury to skeletal muscle fibers of mice following lengthening contractions. *J. Appl. Physiol.* 59:119–126, 1985.
48. MOORE II, D. H. A study of age group track and field records to relate age and running speed. *Nature* 253:264–265, 1975.
49. PHILLIPS, S. K., S. A. BRUCE, and R. C. WOLEDGE. In mice, the muscle weakness due to age is absent during stretching. *J. Physiol. (Lond.)* 437:63–70, 1991.
50. QUETELET, L. A. J. Sur l'homme et le développement de ses facultés. In: *L. Hauman and Cie*, Vol. 2, Paris: Bachelier, Imprimeur-Libraire, 1835, pp. 63–77.
51. RANATUNGA, K. W. The force-velocity relation of rat fast- and slow-twitch muscles examined at different temperatures. *J. Physiol. (Lond.)* 351:517–529, 1984.
52. ROBBINS, A. S., L. Z. RUBENSTEIN, K. R. JOSEPHSON, B. L. SCHULMAN, D. OSTERWEIL, and G. FINE. Predictors of falls among elderly people. *Arch. Int. Med.* 149:1628–1633, 1989.
53. SCHULZ, R. and C. CURNOW. Peak performance and age among superathletes: Track and field, swimming, baseball, tennis, and golf. *J. Gerontol.* 43:P113–P120, 1988.
54. STONES, M. J. and A. KOZMA. Adult age trends in record running performances. *Exp. Aging Res.* 5:407–416, 1980.
55. TINETTI, M. E., T. F. WILLIAMS, and R. MAYEWSKI. Falls risk index for elderly patients based on number of chronic disabilities. *Am. J. Med.* 80:429–434, 1986.
56. VANDERVOORT, A. A., J. F. KRAMER, and E. R. WHARRAM. Eccentric knee strength of elderly females. *J. Gerontol.* 45:B125–B128, 1990.
57. VANDERVOORT, A. A. and A. J. MCCOMAS. Contractile changes in opposing muscles of the human ankle joint with aging. *J. Appl. Physiol.* 61:361–367, 1986.
58. WHIPPLE, R. H., L. I. WOLFSON, and P. M. AMERMAN. The relationship of knee and ankle weakness to falls in nursing home residents: an isokinetic study. *J. Am. Geriatr. Soc.* 35:13–20, 1987.

59. WHITE, T. P., K. I. CLARK, and S. C. KANDARIAN. Mass, fiber number, and cross-sectional area of hindlimb skeletal muscles from C57BL/6 mice at 12 and 28 months of age. *Physiologist* 29:151, 1986.
60. YOUNG, A. M. STOKES, and M. CROWE. Size and strength of the quadriceps muscle of old and young women. *Eur. J. Clin. Invest.* 14:282–287, 1984.
61. YOUNG, A., M. STOKES, and M. CROWE. The size and strength of the quadriceps muscle of old and young men. *Clin. Physiol.* 5:145–154, 1985.
62. ZERBA, E., T. E. KOMOROWSKI, and J. A. FAULKNER. The role of free radicals in skeletal muscle injury in young, adult, and old mice. *Am. J. Physiol.* 258:C429–C435, 1990.
63. ZHANG, Y. L. and S. G. KELSEN. Effects of aging on diaphragm contractile function in golden hamsters. *Am. Rev. Respir. Dis.* 142:1396–1401, 1990.