Effects of Ageing on the Motor Unit: A Brief Review

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Abstract/Résumé

This review briefly summarizes the current state of knowledge regarding age related changes in skeletal muscle, followed by a more in-depth review of ageing effects on animal and human motor units (MUs). Ageing in humans is generally associated with reductions in muscle mass (atrophy), leading to reduced voluntary and electrically evoked contractile strength by the 7th decade for most muscle groups studied. As well, contraction and one-half relaxation times are typically prolonged in muscles of the elderly. Evidence from animal and human studies points toward age associated MU loss as the primary mechanism for muscle atrophy, and such losses may be greatest among the largest and fastest MUs. However, based on studies in animals and humans, it appears that at least some of the surviving MUs are able to partially compensate for MU losses, as indicated by an increase in the average MU size with age. The fact that muscles in the elderly have fewer, but on average larger and slower, MUs has important implications for motor control and function in this population.

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Le but de cet article est de présenter un sommaire des connaissances acquises au sujet des effets de l'âge sur le muscle squelettique et de donner un compte rendu plus détaillé des effets de l'âge sur l'unité motrice des animaux et des êtres humains. Le vieillissement de l'être humain se manifeste généralement par une diminution de la masse musculaire (atrophie) qui se traduit à la septième décennie par une perte de force musculaire sollicitée volontairement ou électriquement dans la majorité des groupes musculaires évalués. En outre, le temps de contraction et le temps de demi-relaxation sont typiquement augmentés chez les personnes âgées. Des études réalisées tant chez les animaux que les humains suggèrent que l'atrophie musculaire est causée par une perte d'unités motrices surtout parmi les plus grosses et les plus rapides. D'autres études cependant soulignent que certaines unités motrices restantes semblent réagir à cette perte par une augmentation de leur taille moyenne avec l'âge. Les implications d'une réduction du nombre d'unités motrices et de l'augmentation de leur taille moyenne sur le contrôle neuromoteur chez la personne âgée sont certainement importantes.

Introduction

Ageing in humans is generally associated with a substantial decline in neuromuscular performance (for our purposes, ageing, age related, and age associated refer to changes that occur in the motor system beyond adulthood). Characteristic of this decline in humans is an age related reduction in skeletal muscle mass, leading to decreased voluntary and electrically evoked contractile strength (Grimby and Saltin, 1983; Larsson, 1982; Lexell, 1993; Rogers and Evans, 1993; Vandervoort, 1992). A considerable body of experimental evidence suggests that these age associated reductions in muscle mass are primarily a consequence of losses of alpha motor neurons in the spinal cord, and secondary denervation of their muscle fibres (Campbell et al., 1973; Doherty and Brown, 1993b; Doherty et al., 1993; Gutmann and Hanzlikova, 1972; Lexell, 1993; McComas et al., 1971b; Spencer and Ochoa, 1981). Thus the motor unit (MU) pool to a given muscle would be expected to undergo substantial degeneration and reorganization following these neurodegenerative processes.

The MU, originally described by Sherrington and colleagues (Eccles and Sherrington, 1930; Liddell and Sherrington, 1925), is the basic functional component of the mammalian motor system. It is comprised of an α motor neuron with its cell body in the ventral horn of the spinal cord, its single motor axon, and all of the muscle fibres innervated by the axon. Activation of MUs in response to signals from higher brain centers, or inputs from the periphery, governs the voluntary and reflex recruitment of motor neurons underlying all postural and movement related contractions (Burke, 1981; Freund, 1983; Stuart and Enoka, 1983).

The impact of ageing on the physiological properties of MUs has been investigated extensively in animal studies, most of which have focused on the rat hindlimb muscles. On the other hand, probably because of previous technical challenges and limitations imposed on studying the electrophysiological and contractile properties of single human MUs in vivo, past research on humans has been limited. However, a growing body of literature, including some of our own work, has shed considerable light on this topic and provided much insight into the potential mechanisms underlying age related changes at the whole muscle level.

The following comprises a brief review of age related changes in human skeletal muscle and a more detailed analysis of ageing effects on animal and human MUs. The reader is directed, where deemed appropriate, to other recent reviews of the literature, and an attempt has been made to synthesize the findings of studies performed at the whole muscle level with studies in animals and humans that have investigated age related changes at the level of the MU.

Age Related Changes in Human Skeletal Muscle

MUSCLE STRENGTH AND CONTRACTILE PROPERTIES

Atrophy and weakness are common features of skeletal muscle in aged men and women, and these topics have been the focus of considerable study in the past two decades (Grimby and Saltin, 1983; Larsson, 1982; Lexell, 1993; Rogers and Evans, 1993; Vandervoort, 1992). With respect to maximal isometric strength, a variety of limb muscles have been tested in young, middle-aged, and older men and women (Table 1). The results, for the most part, demonstrate reductions in voluntary strength that become substantial by the 7th decade of life and may accelerate thereafter (Rogers and Evans, 1993; Vandervoort, 1992).

The majority of studies in this area have used a cross-sectional design, but longitudinal studies have usually shown similar age associated reductions in strength (Aniansson et al., 1986; 1992; Kallman et al., 1990). However, one recent report by Bassey and Harries (1993) indicated that the loss of handgrip strength over time may be underestimated by the results of cross-sectional studies, and Grieg et al. (1993) found almost no reduction in knee extensor strength over about 8 years in men and women with a median age of 81 years (Table 1).

Healthy men and women in their 7th and 8th decades demonstrate, on average, reductions of 20 to 40% in maximal isometric strength as compared to young adults (Davies et al., 1986; Doherty et al., 1993; Kallman et al., 1990; Larsson et al., 1979; McDonagh et al., 1984; Vandervoort and McComas, 1986; Young et al., 1984, 1985). Despite slight differences between different muscle groups and studies, these age associated reductions are similar for both sexes and for proximal and distal muscles of the upper and lower limbs (see also Table 1 in Vandervoort, 1992).

Studies using concentric (shortening) contractions have also shown an age associated trend with reductions in strength on the order of 20 to 40% for men and women for isokinetic knee extension (Larsson et al., 1979; Murray et al., 1980; 1985) and ankle plantar flexion (Cunningham et al., 1987). Evidence of greater relative decrements in strength on isokinetic testing at higher angular velocities has been reported by some investigators (Cunningham et al., 1987; Larsson et al., 1979; Overend et al., 1992a), whereas others have found similar age associated reductions regardless of the angular velocity (Aniansson et al., 1981; 1986; 1992; Poulin et al., 1992). (Also see Table 1.) Additionally, it has been reported that decrements in strength between young and old are less marked during isokinetic eccentric contractions than for the concentric condition. These observations held for both the elbow and knee extensor muscles in men (Poulin et al., 1992) and the knee extensors and flexors in women (Vandervoort et al., 1990).

The extent to which these reductions in isometric and isokinetic strength reflect a failure to fully activate spinal motor neurons, as opposed to simple

Table 1 Effects of Ageing on Measures of Isometric and Isokinetic Voluntary Strength

Author(s)	Sex	Age (decade)	Condition	Study design	% of Young adults[a]
Knee extension					
Larsson et al. (1979)	M	7th	Isometric	Cross-sectional	75
Murray et al. (1980)	M	8–9th	Isometric	Cross-sectional	55
Murray et al. (1985)	F	8–9th	Isometric	Cross-sectional	63
Young et al. (1984)	F	8th	Isometric	Cross-sectional	65
Young et al. (1985)	M	7th	Isometric	Cross-sectional	61
Overend et al. (1992a)	M	7–8th	Isometric	Cross-sectional	76
			Isokinetic 120°/s	Cross-sectional	68
Poulin et al. (1992)	M	7–8th	Isokinetic 90°/s	Cross-sectional	
			concentric		68
			eccentric		81
			Isokinetic 180°/s		
			concentric		69
			eccentric		98
Aniansson et al. (1986)	M	8–9th	Isometric	7-yr follow-up	73[b]
			Isokinetic 30°/s		88
			Isokinetic 60°/s		76
			Isokinetic 180°/s		91
Grieg et al. (1993)	M,F	8–9th	Isometric	8-yr follow-up	97[b]
Ankle plantarflexion					
Davies et al. (1986)	M	7–8th	Isometric	Cross-sectional	62
	F	7–8th	Isometric	Cross-sectional	72
Petrella et al. (1989)	M	7–8th	Isometric	Cross-sectional	57
Vandervoort & McComas (1986)	M	9–10th	Isometric	Cross-sectional	55
	F	9–10th	Isometric	Cross-sectional	45
Cunningham et al. (1987)	M	7th	Isokinetic	Cross-sectional	
			30°/s		92
			60°/s		77
			90°/s		66
			120°/s		69
			180°/s		44

(cont.)

Table 1 (Cont.)

Author(s)	Sex	Age (decade)	Condition	Study design	% of Young adults[a]
Elbow flexion					
McDonagh et al. (1984)	M	7–8th	Isometric	Cross-sectional	80
Doherty et al. (1993)	M,F	7–8th	Isometric	Cross-sectional	66
Grip strength					
Fisher & Birren (1947)	M	6–7th	Isometric	Cross-sectional	83
Kallman et al. (1990)	M	6th	Isometric	Cross-sectional	91
				9-yr follow-up	93[b]
		7th		Cross-sectional	84
				9-yr follow-up	85
		8th		Cross-sectional	72
				9-yr follow-up	75
		9th		Cross-sectional	63
Bassey & Harries (1993)	M	8th	Isometric	Cross-sectional	8[c]
				4-yr follow-up	12[b]
	F	8th	Isometric	Cross-sectional	7
				4-yr follow-up	19

[a]Values for elderly group expressed as % of younger groups' mean score; [b]values are % of previous score; [c]predicted loss in strength over 4 yrs based on cross-sectional data.

muscle atrophy, is not completely understood. Vandervoort and McComas (1986) have shown that healthy elderly men and women between 60 and 100 years of age, at least for isometric contractions, were able to maximally activate their ankle plantar and dorsiflexor muscles since a supramaximal shock applied to the motor nerve failed to increase maximal voluntary contraction force in most cases (Belanger and McComas, 1981). Alternatively, there is evidence that aged muscle may demonstrate reduced force per unit cross-sectional area, or specific tension, as has been demonstrated for human muscle (Bruce et al., 1989; Klitgaard et al., 1990; Phillips et al., 1992; Vandervoort and McComas, 1986; Young et al., 1985) and rodent muscle (Brooks and Faulkner, 1988; Carlson and Faulkner, 1988). However, the mechanisms for these proposed differences in specific tension are as yet undiscovered, and formidable methodological hurdles face any attempt to completely resolve this question in humans.

With regard to electrically evoked isometric contractile properties of human muscles, a number of studies have reported reductions in the maximal twitch tension and, in many cases, prolonged contraction and one-half relaxation times in the elderly (Campbell et al., 1973; Davies et al., 1986; Doherty et al., 1993;

Keh-Evans et al., 1992; Klein et al., 1988; Vandervoort and Hayes, 1989; Vandervoort and McComas, 1986). (Also see Table 2.) Additionally, Narici et al. (1991) reported an age associated shift in the force/stimulus frequency relationship for the adductor pollicis muscle such that aged muscle exhibited greater partially fused tetanic forces at lower stimulus frequencies.

The extent to which these findings on whole muscles in the elderly reflect alterations in the underlying proportions of slow and fast MUs, generalized changes in the intrinsic contractile properties (myosin heavy chain, sarcoplasmic reticulum) of all muscle fibres, or both, is not completely understood. However, histochemical studies on human muscles and physiological and histochemical studies in animals have provided considerable insight into these questions (see following sections).

MUSCLE MASS AND FIBRE COMPOSITION

Numerous studies have investigated effects of ageing on the quantity and fibre type composition of human skeletal muscle (Lexell, 1993; Rogers and Evans, 1993; Taylor et al., 1992). Although the findings of these studies are generally in agreement, some controversy remains with regard to the underlying mechanisms and expected fibre type composition of skeletal muscles in older men and women.

Age associated reductions in whole muscle cross-sectional area and volume have been demonstrated by studies employing radiological imaging techniques. Young et al. (1984, 1985), using ultrasound, reported 25 to 35% reductions in the total knee extensor cross-sectional area for older (70–79 yrs) men and women as compared to the young (21–28 yrs). Through computed tomography scanning, similar age associated reductions in muscle cross-sectional area have been shown for the quadriceps femoris (Klitgaard et al., 1990; Overend et al., 1992b), brachial biceps (Klitgaard et al., 1990; Rice et al., 1989) and triceps (Rice et al., 1989), and plantar flexor muscles (Rice et al., 1989). As well, studies have reported significant increases in the quantity of nonmuscle tissue within the boundaries of older muscles (Overend et al., 1992b; Rice et al., 1989). For example, along with reductions of 35% in the average cross-sectional area of the plantar flexor muscles of elderly men (65–90 yrs), Rice et al. reported an 81% increase in the quantity of nonmuscle tissue within the plantar flexor compartment. Additionally, Overend et al. reported reductions of 27% and 18%, respectively, for the quadriceps and hamstring muscles of elderly men (65–77 yrs), along with increases in nonmuscle tissue of 59% (quadriceps) and 127% (hamstrings).

In an attempt to gain a better understanding of the mechanisms responsible for the reported age associated reductions in muscle mass and alterations in muscle contractile properties, investigators have employed needle biopsy techniques or studied whole muscle cross-sections postmortem in subjects of different ages. From these studies there is general agreement that the cross-sectional areas of type II fibres are significantly reduced with ageing, while those of type I fibres are less affected (Aniansson et al., 1981; 1986; Grimby et al., 1982; Jennekens et al., 1971; Larsson et al., 1978; Lexell et al., 1988; Nygaard and Sanchez, 1982; Oertel, 1986; Tomonaga, 1977). The reductions in fibre size, however, are considered moderate in comparison with the reductions in muscle mass, and therefore reductions in muscle fibre number have been proposed (Grimby and Saltin, 1983).

Table 2 Age Related Changes in Human Electrically Evoked Isometric Muscle Contractile Properties

Author(s)	Muscle group	Age	Pt	CT	1/2 RT	M-potential
Campbell et al. (1973)	EDB	3 – 58	310 ± 88 g	64 ± 7	53 ± 10	5.7 ± 2.1
		60 – 96	210 ± 131 g	93 ± 22	109 ± 45	2.7 ± 1.7
Cupido et al. (1992)	Tibialis anterior	26.7 ± 1.2	3.2 ± 0.5 Nm	78 ± 3	85 ± 5	9.9 ± 0.6
		67.7 ± 1.7	4.6 ± 0.4 Nm	91 ± 3	102 ± 4	7.9 ± 0.4
Davies et al. (1986)	Triceps surae	21.5 ± 2.4	120 ± 31 N	118 ± 14	82 ± 8	–
		69.7 ± 2.8	96 ± 32 N	147 ± 15	100 ± 17	–
Doherty et al. (1993)	Biceps/brachialis	22 – 38	4.8 ± 2.6 Nm	68 ± 8	130 ± 31	14.5 ± 4.0
		60 – 81	3.2 ± 1.8 Nm	74 ± 13	129 ± 17	9.6 ± 2.8
Klein et al. (1988)	Triceps surae	19 – 32	87 ± 26 N	105 ± 11	91 ± 16	–
		64 – 69	64 ± 13 N	128 ± 15	92 ± 7	–
McDonagh et al. (1984)	Elbow flexor	25.8 ± 6.1	36.4 ± 6 N	64 ± 8	78 ± 2	–
		71.3 ± 3.7	31.7 ± 11 N	71 ± 11	86 ± 11	–
	Triceps surae	25.8 ± 6.1	133 ± 30 N	119 ± 20	–	–
		71.3 ± 6.1	86 ± 26.7 N	146 ± 10	–	–
Petrella et al. (1989)	Gastrocnemius	25.7 ± 3.8	34.4 ± 13 N	101 ± 18	99 ± 35	–
		66.9 ± 5.3	20.5 ± 9.0 N	137 ± 18	123 ± 42	–
Vandervoort and McComas (1986)	Plantarflexors (male)	20 – 32	4.2 ± 1.5 Nm	101 ± 7	84 ± 11	9.4 ± 2.6
		40 – 52	4.5 ± 1.2	111 ± 13	100 ± 15	9.7 ± 1.5
		60 – 69	3.3 ± 1.4	104 ± 11	102 ± 19	7.0 ± 1.9
		70 – 79	3.3 ± 1.3	115 ± 15	122 ± 23	7.8 ± 3.1
		80 – 100	2.6 ± 0.8	125 ± 22	125 ± 32	5.4 ± 1.6
	(female)	20 – 32	2.7 ± 1.3 Nm	96 ± 8	84 ± 13	9.1 ± 2.6
		40 – 52	3.7 ± 0.9	113 ± 10	110 ± 19	10.5 ± 2.3
		60 – 69	2.8 ± 1.0	115 ± 9	120 ± 16	7.9 ± 4.0
		70 – 79	1.8 ± 0.9	110 ± 13	119 ± 28	6.3 ± 2.8
		80 – 100	1.7 ± 0.8	128 ± 10	131 ± 29	5.2 ± 2.0

Note. Data are presented as ranges of values or means ± *SD*, except Cupido et al. (1992) where the *SE* is given. Pt, peak twitch tension; CT, contraction time (ms); 1/2 RT, one-half relaxation time (ms); M-potential, maximum compound muscle action potential amplitude (mV).

Lexell et al. (1988), using whole muscle cross-sections of the vastus lateralis muscle obtained postmortem, found that older subjects in their 80s had about 50% fewer type I and type II muscle fibres when compared with subjects in their 20s. This provides strong evidence for the hypothesis that losses of muscle mass are mainly related to losses of muscle fibres. Furthermore, in contrast to an earlier report based on an examination of needle biopsy tissue in this same muscle (Larsson et al., 1978), Lexell found similar relative losses of type I and type II muscle fibres. Therefore it would appear that the cross-sectional area, at least for the vastus lateralis muscle, is determined largely by the total number of fibres, and to a lesser extent by the size and/or number of type II fibres (Lexell, 1993; Lexell and Downham, 1992).

Alternatively, Klitgaard et al. (1990) compared the myosin heavy chain composition of single muscle fibres obtained through needle biopsy of human vastus lateralis muscle from young and aged men. In younger subjects, the majority of muscle fibres expressed a single isoform of myosin. However, in older subjects a greater proportion of fibres co-expressed type I and IIa, or type IIa and IIb myosin heavy chain isoforms. Their findings provide evidence for transitional changes in myosin heavy chain composition in older muscle, and suggest that histochemical staining for myosin ATPase, as used in most previous studies, may not provide the necessary sensitivity to identify subtle changes in myosin composition. Furthermore, regardless of the sensitivity of the method used for analyzing muscle fibre type composition, these morphological studies provide no indication of the numbers or relative sizes (innervation ratios) of MUs of different physiological types and sizes. Therefore any such changes with ageing in these properties of the MU could be masked.

Evidence of neurodegenerative processes have also been commonly reported in histological studies of muscle from older humans (Grimby, 1988; Jennekens et al., 1971; Lexell, 1993; Lexell et al., 1988; Oertel, 1986; Tomlinson and Irving, 1973; Tomonaga, 1977). Fibre type grouping, fibre atrophy, and irregularly shaped fibres all provide evidence of an ongoing denervation/reinnervation process whereby muscle fibres that have been denervated following loss of their neuromuscular contact are reinnervated by surviving motor neurons (Brown, 1984; Brown et al., 1981). Eventually, reinnervation may fail to keep pace with neurodegenerative processes, and permanently denervated fibres are therefore lost and replaced with fat and connective tissue, thus providing a likely explanation for the age associated reductions in fibre number and increases in nonmuscle tissue. The extent to which these processes equally affect all MUs will be dealt with in the subsequent sections.

Effects of Ageing on the Motor Unit

The motor neuron has been described as the "final common pathway" for the motor system (Liddell and Sherrington, 1925), since activation of motor neurons is responsible for all muscle contractions involved in posture, locomotion, speech, and even facial expression and gesture. The nature of the human motor system is such that it allows healthy individuals to generate muscle contractions ranging from the minute forces and precision necessary for executing fine motor skills, to the maximal ballistic contractions required for executing a sport skill or

recovery from a potential fall. The ability to produce these intended motor outcomes is partially dependent on having a population of MUs varying widely in their sizes and functional characteristics, and the ability to appropriately excite or inhibit them to produce a desired muscle contraction. Therefore, it follows that any age related alteration in the numbers or functional properties of MUs in the pool to a given muscle group may have profound implications for muscle force production and its control.

ANIMAL STUDIES

The muscles in the rat hindlimb have been studied most extensively with regard to age related changes in their MU populations (Faulkner et al., 1990; Larsson, 1982). Although some discrepancies are apparent in the findings, there is general agreement among studies that substantial age related degeneration of the motor neuron is present in the senescent rat. For example, physiologic and morphometric studies have shown significant reductions of 40 to 75% in the estimated number of MUs in the hindlimb muscles of aged rats (Caccia et al., 1979; Edström and Larsson, 1987; Einsiedel and Luff, 1992a; Pettigrew and Gardiner, 1987). Additionally, the numbers of motor neurons in a given MU pool, as determined by horseradish peroxidase labelling, have been found to be reduced in aged rats using morphometric techniques (Hashizume et al., 1988; Ishihara and Araki, 1988; Ishihara et al., 1987).

For the most part, these studies have shown greater losses among the largest α motor neurons which correlated well with selective losses and degeneration of the largest myelinated axons (Ansved and Larsson, 1990; Hashizume et al., 1988; Knox et al., 1989). For example, Ishihara and associates (1987, 1988) reported reductions in the numbers of fast glycolytic muscle fibres in adult muscles with no apparent loss of slow oxidative or fast oxidative glycolytic muscle fibres. Furthermore, old rats (30–33 mos) exhibited reduced numbers of motor neurons, which were greatest for the largest motor neurons with the lowest oxidative enzyme capacities. These results may suggest early preferential degeneration of the largest motor units, with the largest innervation ratios, followed by a preferential loss of these MUs in old age.

There is also evidence that MUs from aged mice (Jacob and Robbins, 1990a, 1990b) and rats (Einsiedel and Luff, 1992b; Fagg et al., 1981; Gutmann and Hanzlikova, 1966, 1972; Kelly, 1978) have reduced capacity for reinnervation or a reduced safety factor for neuromuscular transmission (greater incidence of transmission failure) following partial denervation. Older motor neurons, therefore, have a reduced capacity to take on and maintain an increased field of functional innervation. These findings, which may be related to the motor neuron's reduced capacity to supply acetyl-choline or other as of yet undescribed trophic substances to a greatly enlarged peripheral field, likely contribute to the eventual loss of fibres observed in aged muscle (McComas, 1977).

The physiological, histochemical, and immunohistochemical properties of rat hindlimb muscles undergo substantial age related changes as well, many of which may be secondary to the previously mentioned neurodegenerative processes. As described earlier for humans, muscles of the aged rat hindlimb exhibit substantial atrophy, probably due to losses of muscles fibres (Ansved and Larsson, 1989; Caccia et al., 1979; Ishihara and Araki, 1988; Ishihara et al., 1987; Kanda and Hashizume, 1989; Larsson and Edström, 1986; Pettigrew and Gardiner,

1987). Additionally, muscle-to-body-mass ratios have been shown to decline with old age in most studies (Edström and Larsson, 1987; Einsiedel and Luff, 1992a; Larsson et al., 1991; Pettigrew and Gardiner, 1987; Pettigrew and Noble, 1991), due to concomitant increases in body weight. Taken together with the aforementioned neurodegenerative changes, these results imply that fewer motor neurons, innervating less total muscle mass, are available to overcome substantially greater relative loads.

In contrast to studies in human muscle, it is generally agreed that there is an increase in the proportion of muscle fibres expressing type I myosin as determined by ATPase staining in hindlimb muscles from aged rats. For the most part, studies have shown increases in the total muscle cross-sectional area composed of type I fibres, at the expense of type IIa and IIb fibres (Caccia et al., 1979; Edström and Larsson, 1987; Einsiedel and Luff, 1992a; Ishihara and Araki, 1988; Ishihara et al., 1987; Larsson and Edström, 1986; Pettigrew and Gardiner, 1987).

In an attempt to provide a mechanism for these findings, studies have employed single motor unit glycogen depletion techniques, followed by histochemical staining for fibre type (Kugelberg and Edström, 1968). Increases in the innervation ratios of slow twitch MUs in older animals, in the face of overall lower numbers of muscle fibres and particularly the losses of fast twitch fibres, provide sound evidence for a fast-to-slow myosin conversion following partial reinnervation (Edström and Larsson, 1987; Kanda and Hashizume, 1989). Further evidence for a fast-to-slow conversion of muscle fibre types comes from studies employing monoclonal antibodies to myosin heavy chain. Larsson et al. (1991; 1993) have shown increases in the novel IIX myosin heavy chain isoform in aged rat tibialis anterior muscles and suggest that IIX MUs may represent a transitional motor unit type involved in an age related fast-to-slow conversion process.

The contractile properties of hindlimb muscles from aged rodents for the most part parallel the findings on human muscle reported earlier. For example, both Caccia et al. (1979) and Brooks and Faulkner (1988) reported that the contraction times (CT) and one-half relaxation times (1/2 RT) were prolonged for the "slow" soleus muscle, whereas Larsson and Edström (1986) reported increases only for the contraction times of this muscle. Larsson and Edström also reported age related increases in the contraction time for the "fast" tibialis anterior muscle.

The time-course of the contractile response in a whole muscle depends on the composition of the MU pool and the properties of the individual MUs. The contractile properties of single MUs are determined by a series of events in the excitation/contraction coupling process of their constituent muscle fibres. The capacity of the sarcoplasmic reticulum for calcium release and uptake, and the composition of fast and slow isoforms of the myofibrillar proteins, are the main factors that determine the contractile speed of the MU (Larsson and Edström, 1986). Any significant age associated increase in the percentage of MUs with slow contractile properties, or an overall slowing of all the MUs in a muscle, may serve to prolong the twitch contraction time.

Both mechanisms potentially contribute to the prolonged twitch durations reported for whole muscles. For example, studies have shown increases in the contraction times (CTs) and/or one-half relaxation times (1/2 RTs) for MUs

characterized as having either fast or slow MU properties (most often defined as per Burke et al., 1973). Using these methods, Pettigrew and Gardiner (1987) reported increases in CTs with no apparent increase in the 1/2 RTs for MUs in the plantaris muscles of senescent rats. On the other hand, Edström and Larsson (1987) reported increases in both the CTs and 1/2 RTs for MUs in the predominantly slow soleus and the fast tibialis anterior muscle. In fast MUs, a potential underlying mechanism of the reported age related decrease in the speed of contraction is the decrease in the volume and intrinsic function of the sarcoplasmic reticulum (Larsson and Salviati, 1989). However, this mechanism does not appear to explain reported differences in slow MUs.

The altered contractile properties in aged rat hindlimb muscles, however, are not simply a function of prolonged twitch durations in the constituent MUs. As reported earlier, ageing is associated with significant losses of MUs and shifts in the relative proportions of muscle fibres expressing fast and slow myosin isoforms. Evidence for selective losses of the largest, fastest MUs are supported by the results from physiological studies of MU contractile properties in rat hindlimb muscles. For example, Pettigrew and Gardiner (1987) reported decreased tetanic tension (Po), an increased ratio of twitch to tetanic tension (Pt/Po), and a significantly prolonged 1/2 RT in whole plantaris muscles of older rats. Underlying these changes in the whole muscle were substantial losses of MUs (40%) and a marked increase in the mean Po and proportion of slow MUs in this muscle. Similarly, Kanda and Hashizume (1989) reported significant age associated reductions in the mean Po of fast fatigable, fast intermediate, and fast resistant MUs, while the mean Po of slow MUs was substantially increased. An increase in the innervation ratio of slow MUs was the likely mechanism for the age associated increases in their tetanic tensions.

Pettigrew and Noble (1991) support these findings and provide evidence for an increase in the numbers of slow, and what they refer to as "transitional," MUs in the plantaris muscles from older rats. Increases in the percentage of slow and transitional MUs in the plantaris occurred at the expense of fast fatigable MUs in adult rats (14 mos), and later at the expense of fast intermediate MUs in old rats (24 mos). MUs with transitional properties likely arose when multiple isoforms of myosin were expressed in the constituent muscle fibres of MUs in the older animals (cf. Larsson et al., 1991; 1993).

Taken together, these results point toward an age associated reorganization of the motor unit pool, whereby selective losses or degeneration of the fastest MUs are accompanied by increases in the proportion of slow and transitional MUs. The greater success of slow MUs in partially reinnervating muscle fibres that have become denervated following the loss of their parent motor neurons, and the possible change in the recruitment patterns of the remaining MUs, may possibly explain the apparent shifts in the physiological properties of the MU pool to a given muscle in the rat hindlimb.

CHANGES IN HUMAN MOTOR UNITS

Indirect evidence for age related changes in the numbers and physiological properties of human MUs has come from studies of whole muscle contractile function and analysis of muscle fibres from biopsy samples or whole muscle sections obtained postmortem; the results of these studies have been briefly reviewed in the previous sections. However, other more direct evidence comes

from morphometric studies of anterior horn cells and ventral root or peripheral nerve fibres, and from physiologic studies of single MU electrophysiological and contractile properties. Very few human studies, however, have investigated the latter.

The work of Tomlinson and Irving (1977) provided one of the more thorough investigations of the numbers of motor neurons innervating human limb muscles in different age groups. They studied, postmortem, the lumbosacral spinal cords (L1–S3) of 47 subjects between 13 and 95 years of age, and found that, although individual counts varied considerably in all age groups, there was no evidence of reduced numbers of motor neurons up to 60 years of age. Beyond 60 years, however, there were significant reductions in motor neuron numbers, with several cases exhibiting counts at only 50% of those found in young or middle-aged subjects. Without longitudinal data, however, the extent to which low counts actually reflect greater cell losses in individual cases, as opposed to actual variability in the numbers of motor neurons present in any age group, is uncertain.

The only other observation of note in their study was the increased accumulation of lipofuscin in motor neurons with increasing age. Lipofuscin, a pigment derived by oxidation of lipid or lipoprotein sources, is thought to be the most reliable and widespread cytological change correlated with neuronal ageing. Excessive accumulation of lipofuscin may apparently precipitate neuronal degeneration; however, it is unlikely to be solely responsible for losses of cells in the peripheral nervous system (Spencer and Ochoa, 1981). Neurofibrillary tangles, on the other hand, which are typical of ageing in cortical neurons, are seldom present in anterior horn cells (Spencer and Ochoa, 1981).

Kawamura et al. (1977a) estimated, postmortem, the numbers and sizes of motor axons in the lumbar (L3, L4, and L5) ventral roots from 17 subjects between 17 and 81 years of age. There were definite age associated reductions in the numbers of large and intermediate ventral root fibres, with no significant reductions reported for the small fibres. The extent to which these findings truly represented α motor neuron losses, as opposed to shifts in the distribution of large and small fibres with ageing, was supported in a subsequent study by this group (Kawamura et al., 1977b). In the latter study, similar age related cell losses were shown for the L3, L4, and L5 motor neuron columns of the spinal cord. These results are similar to previous early studies in which, by age 89, a 32% reduction in thoracic ventral root axons was reported along with an increase in the amount of connective tissue (Corbin and Gardner, 1937; Gardner, 1940). Additionally, Mittal and Logmani (1987) have observed not only reductions in the number of myelinated large nerve fibres in the 8th cervical ventral root but also an overall reduction in fibre diameter. Taken together, these findings point toward definite age associated losses of alpha motor neurons and the subsequent degeneration of their axons.

The health and integrity of the peripheral motor system is often assessed clinically by measuring the maximal motor conduction velocity (CV) of a given nerve. It is well established, using conventional techniques, that motor nerve conduction velocities decrease progressively, albeit moderately, with age (Dorfman and Bosley, 1979; Falco et al., 1992; Norris et al., 1953; Schaumburg et al., 1983). Based on standard nerve conduction methods, these reductions could be the result of selective losses of the largest and fastest conducting motor fibres,

losses of the same fibres through natural random attrition, or even uniform slowing of the motor axon CVs of all nerve fibres.

Using a technique based on impulse collision (Thomas et al., 1959), Campbell et al. (1973) reported that the difference in latency between the slowest and fastest conducting nerve fibres in the common peroneal nerve to the extensor digitorum brevis muscle (located on the dorsum of the foot) was several times greater than the range in latency in young subjects. It was suggested that this slowing likely occurred at the ankle, as normal values were found for the segment between the ankle and knee. Additionally, Arasaki et al. (1991), using a computerized collision method (Nakanishi et al., 1986), found that both maximal and minimal motor conduction velocities in the ulnar nerve were reduced with increasing age.

These results are confirmed and extended by the findings of our study (Doherty and Brown, 1993a) in which we have examined the range and distribution of CVs of single median motor fibres in young and older subjects using a computerized technique based on the F-response (cf. Fisher, 1992). Our findings suggest that the axonal CVs of all motor nerve fibres were uniformly slowed with ageing, such that younger subjects had a range of motor unit CVs from 48 to 68 m/s (mean 59 ± 4) and subjects in their 7th and 8th decades exhibited a range of values from 38 to 61 m/s (mean 52 ± 3) (Figure 1).

Morales et al. (1987) reported remarkably similar findings in MUs from aged cat medial gastrocnemius muscles studied with intracellular recording and stimulating techniques. They found a similar reduction in the entire distribution of motor axon CVs in the older cats, rather than a selective loss of the fastest conducting axons or a predominance of slowly conducting axons. On the other hand, Kanda and Hashizume (1989) reported that although all rat medial gastrocnemius MU types expressed significant age related reductions in axonal CVs, there were greater relative losses of the faster conducting fibres. The extent to which these opposing results reflect inconsistencies between differing species is unknown.

The cause of such generalized reductions in motor axon CVs with ageing in humans might reflect a variety of changes in the underlying nerve fibres; direct evidence of pathological changes includes dropout of the largest fibres, degeneration of fibres, segmental demyelination and remyelination (Arnold and Harriman, 1970; Dyck, 1975; Ochoa and Mair, 1969), and reduced internodal length (Arnold and Harriman, 1970; Lascelles and Thomas, 1966; Stevens et al., 1973).

A number of investigators have studied the muscles of healthy older subjects with quantitative electromyography (EMG), and for the most part rather modest age related changes in motor unit action potentials (MUAPs) have been reported. Sacco et al. (1962) reported minor yet significant increases in the mean MUAP duration and amplitude in the biceps brachii and abductor digiti quinti muscles. Alternatively, Campbell et al. (1973) studied the extensor digitorum brevis muscle of elderly subjects, a muscle known to express early histological signs of partial denervation and reinnervation (Jennekens et al., 1972). They found only a small increase in the mean MUAP duration and no significant increase in the mean MUAP amplitude.

Studies of this nature were limited for the most part to low threshold MUs, which may not have been entirely representative of age related changes in the full

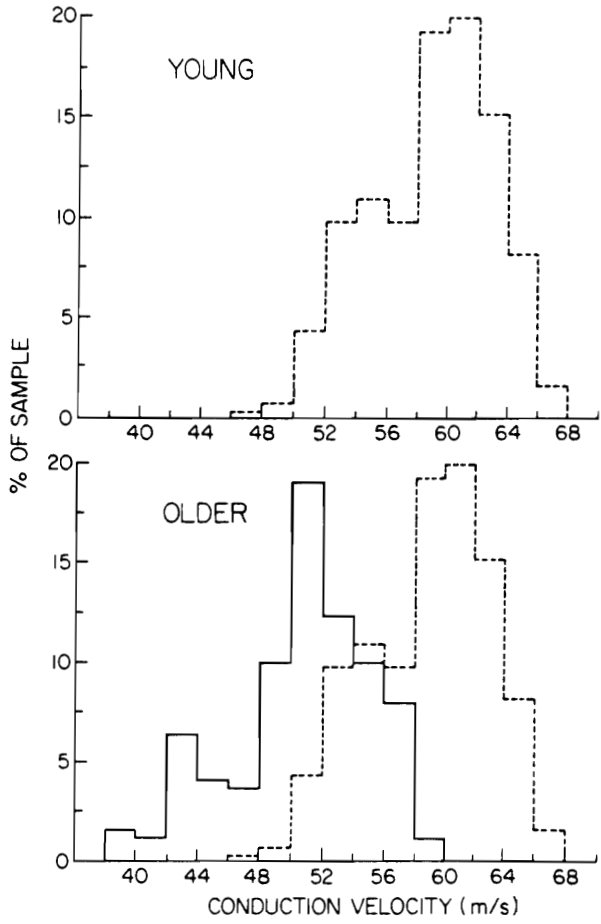

Figure 1. Distribution of median motor axon conduction velocities in younger (24–53 yrs) and older subjects (64–74 yrs) (superimposed over that for the young). From "Physiological properties of single thenar motor axons in the F-response of younger and older adults" by T.J. Doherty, T. Komori, D.W. Stashuk, A. Kassam, and W.F. Brown, *Muscle Nerve*, in press. Copyright © John Wiley & Sons, Inc. Reprinted by permission.

recruitment continuum of MUs in a particular muscle. Subsequent investigations, however, employed computer-assisted automated analysis of the needle-detected EMG signal, allowing the study of higher recruitment threshold MUs (Dorfman and McGill, 1988). For example, Hayward (1977) reported increases in the mean MUAP amplitude for the biceps brachii and tibialis anterior muscles, with no increase in turns count (a measure of the complexity of the interference pattern, indicative of denervation/reinnervation processes) in response to standard loads

approximating 10 to 20% of maximum voluntary contraction force. Howard et al. (1988) used an automated EMG decomposition algorithm and reported progressive increases with age in mean MUAP duration and number of turns in response to controlled contractions between 10 and 30% of maximum for the brachial biceps, triceps, and tibialis anterior muscles. These results are suggestive of an ongoing denervation/reinnervation process that contributes to increases in the numbers of muscle fibres per recruited MU, or increases in "fibre density" within the detection zone of the concentric needle electrode.

The amplitude of the spike component of the MUAP detected in conventional EMG with a concentric needle electrode represents only a small portion of the muscle fibres in a MU. Action potentials from more fibres, but not all, contribute to the initial and terminal phases of the MUAP from which the duration is determined. Macro EMG (Stålberg, 1980) likely provides a more representative estimate of MU size, since its amplitude or area is determined by more of the constituent fibres in the MU. Stålberg and Fawcett (1982) reported increases, after the age of 60 years, in the macro EMG amplitude for both the tibialis anterior muscle and the vastus lateralis muscle, with no significant increase reported for the biceps brachii muscles.

Similar age related increases in macro EMG amplitude have been reported for the vastus lateralis muscle and tibialis anterior muscle in subsequent investigations (de Koning et al., 1988; Stålberg et al., 1989). These results, again, provide evidence of an age related denervation/reinnervation process such that there are greater numbers of muscle fibres per MU, resulting in larger amplitude potentials. This process may predominantly affect distal muscles (Stålberg, 1982); however, the latter notion remains controversial (see following section).

Age related degenerative changes in the terminal motor innervation of human MUs have also been reported (Spencer and Ochoa, 1981). For example, using light and electron microscopy, Wokke et al. (1990) studied the intercostal muscle end-plate morphology from biopsy material in subjects between 4 and 77 years. Although reporting no increase in terminal sprouting with ageing, nor any age related changes in the area staining for cholinesterase, they reported that end-plates in aged muscle were more complex and irregular along with some muscle fibre type grouping. The lack of increase in terminal sprouting with ageing in this study points toward nodal sprouting (nerve branching that originates from nodes of Ranvier in the distal myelinated portion of the motor axon) from healthy axons as the likely method for reinnervation of muscle fibres following loss of their parent motor neuron (Brown, 1984; Brown et al., 1981).

Studies using single fibre EMG have also provided evidence for some degree of degeneration in neuromuscular transmission. Stålberg and Trontelj (1979) have reported progressive increases in the neuromuscular "jitter" (the variability in transmission time between two muscle fibres in a voluntarily recruited MU) in the tibialis anterior and extensor digitorum communis muscles with ageing. These findings were associated with increases in fibre density, or the number of fibres in the detection area of the single fibre electrode. The impact of such changes, however, does not appear to significantly affect neuromuscular transmission in the healthy elderly, even during high frequency repetitive stimulation, as indicated by maintenance of the surface-detected M-potential amplitude (Cupido et al., 1992).

A number of electrophysiological methods have been established to estimate the numbers of MUs in human muscles (see Doherty et al., in press; McComas, 1991). These methods involve determining the average MU size as represented by the average surface-detected motor unit action potential size (S-MUAP) or twitch tension from a small, but presumably representative, sample of MUs in a muscle or muscle group. Parameter values from the maximum M-potential or twitch contraction resulting from supramaximal stimulation of the motor nerve innervating the muscles are then divided by the corresponding parameter values derived from the average S-MUAP or MU twitch tension to calculate the motor unit estimate (see Figure 2). These methods have been employed to study the

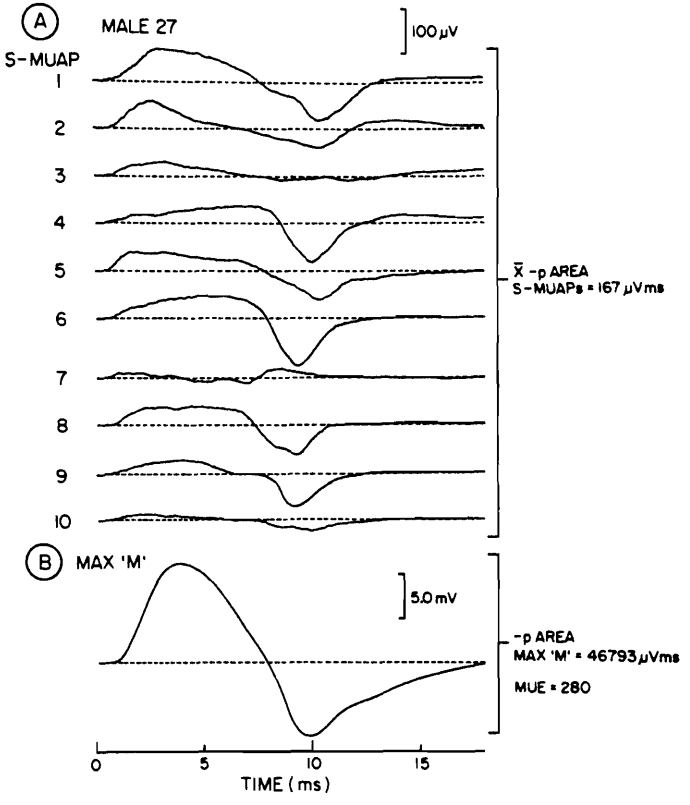

Figure 2. Typical motor unit (MU) number estimate trial using the multiple point stimulation method. Ten surface-detected motor unit action potentials (S-MUAPs) were collected from the thenar muscles in response to electrical stimulation of single thenar motor axons along the course of the median nerve. Their mean negative peak area is 167 μVms, compared to 46,793 μVms for the maximum M-potential. From "The estimated numbers and relative sizes of thenar motor units as selected by multiple point stimulation in young and older subjects" by T.J. Doherty and W.F. Brown, 1993, *Muscle Nerve*, 16: 355-366. Copyright © John Wiley & Sons, Inc. Reprinted by permission.

Table 3 Electrophysiological Estimates of Motor Unit Numbers in Various Muscles of Young and Older Men and Women (means ± *SD*)

Author(s)	Muscle group	Young	Older (>60 yrs)
Brown (1972)	Thenar	253 ± 34	<120
Campbell et al. (1973)	EDB	198 ± 58	<120
Sica et al. (1974)	Thenar	340 ± 87	83 ± 46
	Hypothenar	380 ± 79	177 ± 54
Doherty and Brown (1993b)	Thenar	288 ± 95	139 ± 68
Doherty et al. (1993)	Biceps brachii/brachialis	357 ± 97	189 ± 77

effects of ageing in a number of human muscle groups, and for the most part the results are in agreement with the aforementioned animal studies and the few anatomical studies in humans (see Table 3).

Using the manual incremental stimulation technique first described by McComas et al. (1971a), Brown (1972) reported that control subjects over 60 years of age had less than half the number of MUs in the thenar muscles when compared with younger controls. In this study, subjects under 60 years of age had a mean S-MUAP size of 53 ± 7.9 μV (1 *SD*), whereas subjects with motor unit estimates under 100 had mean S-MUAP sizes of 100 ± 51 μV. Similar results were reported by Campbell et al. (1973) for the extensor digitorum brevis (EDB) muscle, whereby subjects over 60 years of age exhibited substantial losses of MUs and significant increases in the average size of the remaining MUs. Indeed, some healthy older subjects in their study exhibited fewer than 10 functioning MUs, versus a mean of almost 200 in younger subjects.

Sica et al. (1974) reported average MU losses of 77% ± 14, 77% ± 9, and 58% ± 11 for the EDB, thenar, and hypothenar muscles, respectively, in a group of men and women with an average age of 80 ± 7 years. In each case there were significant increases in the average S-MUAP size, along with concomitant reductions in the size of the maximum M-potential. Taken together, these results provide sound evidence for an age associated reduction in the numbers of MUs in distal muscles with the subsequent enlargement of the surviving MUs, most likely through a process of collateral reinnervation (M.C. Brown, 1984; W.F. Brown, 1973; McComas et al., 1971c).

Using an alternative technique based on spike-triggered averaging to extract S-MUAPs from which to derive an average S-MUAP size, Brown et al. (1988) reported that healthy subjects over 60 years of age had approximately half the numbers of MUs in the biceps brachii and brachialis muscles when compared to subjects under 60 years of age. This provided the first evidence of age related MU losses in a larger proximal muscle group innervated by a peripheral nerve not prone to entrapment-type injury. These findings have been supported by our subsequent study (Doherty et al., 1993) in which subjects over 60 years had, on average, 189 ± 77 MUs in the biceps brachii and brachialis muscles whereas young controls had 357 ± 97 MUs. These age related reductions in MU number

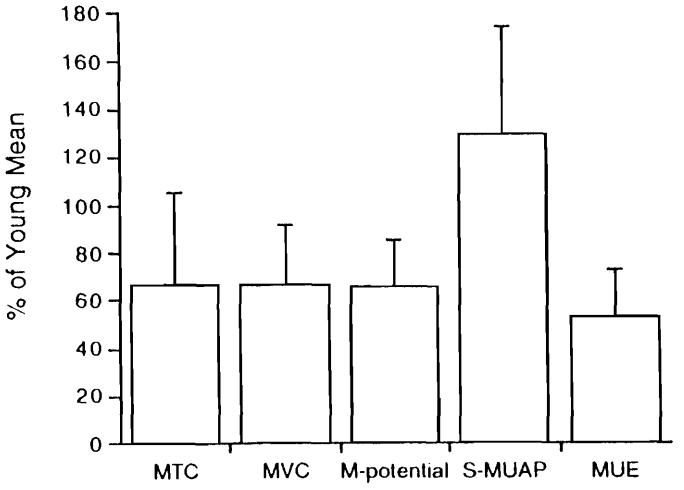

Figure 3. Mean ±*SD* for biceps brachii/brachialis muscles of older subjects (60–81 yrs) plotted relative to younger subjects (22–38 yrs). MTC, max. twitch contraction; MVC, max. voluntary contraction; M-potential, max. compound muscle action potential; S-MUAP, mean surface-detected motor unit action potential amplitude; MUE, motor unit number estimate. Adapted from "Effects of motor unit losses on strength in older men and women" by T.J. Doherty, A.A. Vandervoort, A.W. Taylor, and W.F. Brown, 1993, *J. Appl. Physiol.* 74: 868-874. Copyright © The American Physiological Society. Reprinted by permission.

were accompanied by significant yet less marked reductions in both the maximal twitch and maximal voluntary contractile forces of these muscles (Figure 3).

Furthermore, Doherty and Brown (1993b), using a different method (multiple point stimulation), found similar reductions in the numbers of MUs in the thenar muscles for a similar group of older subjects. These reductions in the estimated numbers of MUs were accompanied by a shift toward greater numbers of larger S-MUAPs in older subjects with a mean S-MUAP amplitude of 84 ± 26 μV in young subjects as compared to 125 ± 55 μV in older subjects. The consistent observation of reduced MU numbers in both distal *and* proximal muscles indicates that damage of the nerve at common peripheral entrapment sites cannot be held solely responsible for age associated MU losses. However, subclinical entrapment of the cervical roots cannot be ruled out as a possible mechanism for MU losses in both cases (Brown, 1987).

Whatever the cause, significant and marked losses of MUs are present in men and women by the 7th decade of life, with possible acceleration of such losses thereafter. Thus, as described earlier for the animal model, it is likely that the remaining MUs in the pool to any muscle group would undergo substantial reorganization with respect to their underlying physiological properties. Results from the aforementioned electrophysiological studies provide evidence for the enlargement of the surviving MUs, most likely through a process of collateral reinnervation as in any neuropathic disorder (Brown et al., 1981; Brown, 1973; McComas et al., 1971c). Few studies, however, have characterized the contractile properties of

single MUs in aged human muscle. Studies of this nature would provide considerable insight with regard to the changes observed at the whole muscle level.

Campbell et al. (1973), in one of the few studies to have measured age related changes in MU contractile parameters, reported that MUs in older subjects often exhibited much larger forces in comparison to young controls. For example, one of the six extensor hallicus brevis MUs examined in older subjects had a twitch tension of 62 g, considerably larger than the upper limit for younger controls (14 g) from an earlier report (Sica and McComas, 1971). Additionally, Newton et al. (1988) found prolonged contraction times in MUs of the first dorsal interosseous muscle along with reductions in the threshold MU firing rate. In the only other known report of single MU contractile force in aged humans, Galganski et al. (1993) reported an increase in the mean twitch tension of first dorsal interosseous MUs, accompanied by a reduced ability to precisely control contractile forces targeted between 5 and 50% of maximum.

For our part, we have completed a study investigating the contractile and electrophysiological properties of single thenar MUs in young and older subjects (Doherty, 1993). Employing force recording methods adapted from those described by Westling et al. (1990), we have used percutaneous stimulation to excite single thenar motor axons and have measured the isometric twitch contractions and S-MUAPs produced by their muscle units (Figure 4). In general, the MUs from older subjects generated larger twitch tensions as reflected by a shift in the frequency distribution toward larger values (Figure 5). Additionally, aged

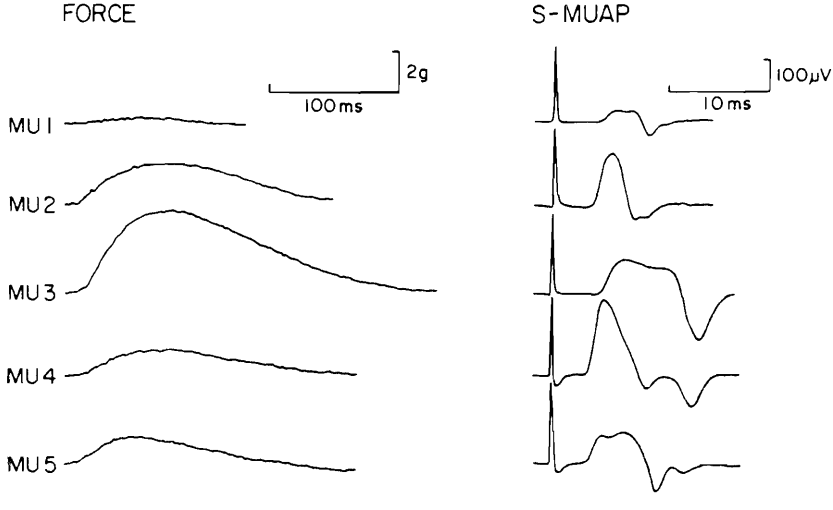

Figure 4. Typical thenar motor unit (MU) twitches and their associated surface-detected motor unit action potentials (S-MUAP) for five MUs (the spike preceding the S-MUAP is the stimulus artifact). Each MU twitch and its associated S-MUAP represent the response to selective stimulation of a single median motor axon at the wrist in a young control subject. The twitch is the resultant composite of the abduction and flexion force components of the thenar MU as detected by two strain gauges applied to the interphalangeal joint of the thumb.

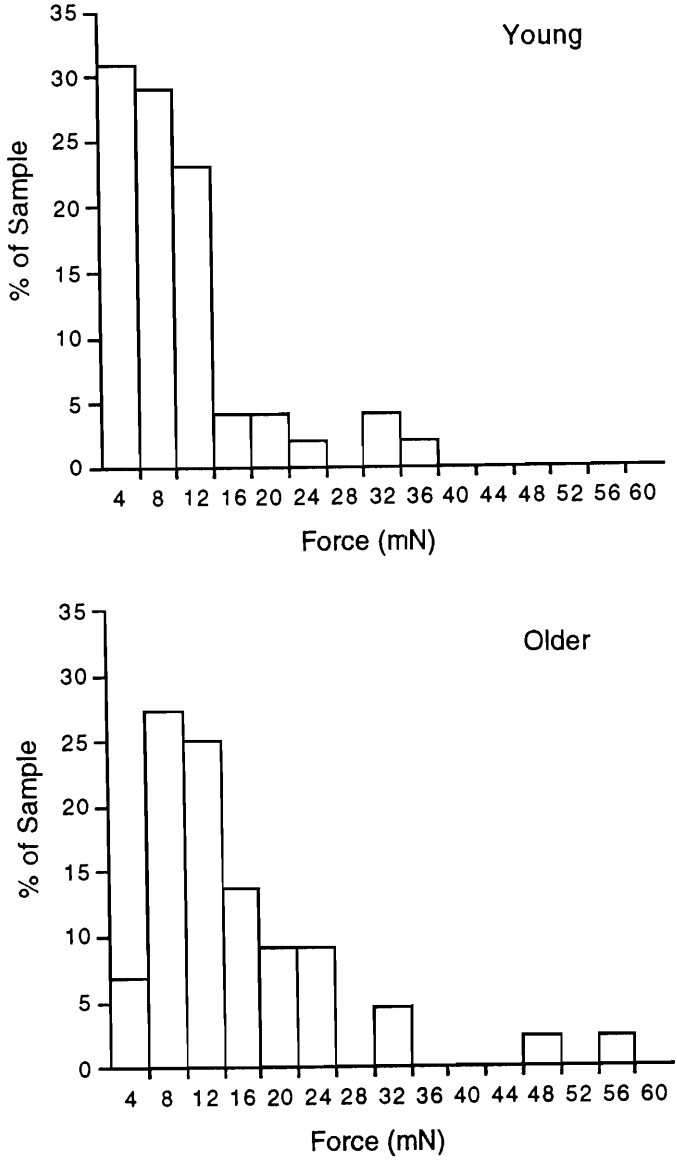

Figure 5. Distribution of the thenar motor unit (MU) twitch forces in younger (25–53 yrs) and older subjects (64–77 yrs) (see Figure 4 for details of data collection). Note the shift in the distribution for older subjects toward greater numbers of larger force MUs (young 1.5–33.2 mN, mean 8.8 ± 7.4; older 2.8–54.8 mN, mean 13.4 ± 10.4).

MUs exhibited significantly prolonged CTs and 1/2 RTs, and, consistent with observations from our earlier study (Doherty and Brown, 1993b), significantly larger S-MUAPs.

Consistent with these differences are the results of a number of studies that have reported decreases in MU firing rates with ageing in both proximal and distal muscles (Borg, 1981; Howard et al., 1988; Nelson et al., 1984; Soderberg et al., 1991). These results are in direct agreement with the reported increases in motor unit CTs and 1/2 RTs in the aforementioned studies and correlate well with studies of whole muscle contractile properties.

Whether the contractile properties of the remaining MUs in aged muscles are modified by changes in the neuromuscular recruitment pattern, or whether motor neuron firing properties are modified to match muscle fibre characteristics, is not completely understood. Regardless, it appears that the reported age related changes in the MU characteristics would indeed provide compensation in the face of substantial MU loss. The fact that the twitch tensions of at least some of the MUs are enlarged, coupled with the fact that they will reach fused tetanic tension more readily due to prolonged CTs and 1/2 RTs, reflects a system capable of producing more force with less central drive. As well, lower fusion frequencies may serve to smooth out the possible loss of fine motor control associated with enlarged MUs following compensatory reinnervation. However, the latter has not been systematically investigated. While these processes may provide some degree of compensation for losses of MUs and muscle mass, there may be a price to pay in the sense that rapid force development, as indicated by prolonged twitch contraction times, is somewhat impaired in the elderly (Vandervoort and Hayes, 1989).

Summary

In summary, it is well established from anatomical and physiological estimates that age related losses of muscle mass and strength in humans are in part secondary to losses of functioning MUs. However, at least some of the remaining MUs are enlarged, most likely through collateral reinnervation, to provide partial compensation for such MU losses. In this fashion, reductions in muscle mass and strength are partially masked in the face of considerable neuronal degeneration. These compensatory processes, however, are not sufficient to keep up with the denervation evident in men and women in their 7th and 8th decades of life. Evidence to this effect has been provided by the reported reductions in maximum strength values, muscle fibre number, and muscle cross-sectional area.

Whether MUs with specific physiological properties are lost in humans, as appears to be true for the rat, remains unclear, as does the extent to which all MUs have similar abilities to compete for denervated fibres. As well, little is known regarding the potential role of exercise as a stimulus to modify the rate or degree to which reinnervation processes are carried out in muscles in the elderly. Convincing evidence has been provided, however, to suggest that the surviving MUs, even in the very old, are capable of adapting to resistance type exercise (Vandervoort, 1992). Given the potential for reductions in muscle mass secondary to losses of MUs, strength training provides an important means of improving the strength and functional capacity of the elderly.

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