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A mini-overview of single muscle fibre mechanics: the effects of age, inactivity and exercise in animals and humans

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Summary

Many basic movements of living organisms are dependent on muscle function. Muscle function allows for the coordination and harmonious integrity of movement that is necessary for various biological processes. Gross and fine motor skills are both regulated at the micro-level (single muscle fibre level), controlled by neuronal regulation, and it is therefore important to understand muscle function at both micro- and macro-levels to understand the overall movement of living organisms.

Single muscle mechanics and the cellular environment of muscles fundamentally allow for the harmonious movement of our bodies. Indeed, a clear understanding of the functionality of muscle at the micro-level is indispensable for explaining muscular function at the macro-(whole gross muscle) level. By investigating single muscle fibre mechanics, we can also learn how other factors such Ca^{2+} kinetics, enzyme activity and contractile proteins can contribute to muscle mechanics at the micro- and macro-levels. Further, we can also describe how aging affects the capacity of skeletal muscle cells, as well as how exercise can prevent aging-based sarcopenia and frailty.

The purpose of this review is to introduce and summarise the current knowledge of single muscle fibre mechanics in light of aging and inactivity. We then describe how exercise mitigates negative muscle adaptations that occur under those circumstances. In addition, single muscle fibre mechanics in both animal and human models are discussed.

Key words: *single muscle fibre mechanics, animal and human muscle cell, exercise, inactivity, aging*

Introduction

Studies related to muscle fibre mechanics generally employ either biomechanical or biochemical analyses. With regard to biomechanical properties, the biophysical plasticity of muscle fibres is typically assessed at the level of a single muscle fibre, with assessments including its strength, endurance and contractile activities. These properties are assessed using a permeabilised, or skinned muscle fibre preparation. These skinned muscle fibres exclude other possible influential factors. For example, surface membrane activation and the degree of calcium ion release from the sarcoplasmic reticulum (inducing excitation-contraction [E-C] coupling, which generates force and contractile velocity [Vo = maximum contractile velocity measured in fibre lengths per second, FL/s] of a muscle fibre and causes a direct interaction between actin and myosin systems via cross bridges) are not included on the biomechanical assessment.

The plasticity of the whole muscle can originate from properties at the single muscle fibre level, but there are multicellular factors that can also play a role. Indeed, factors on both micro- and macroscales, including mechanical force, hormones, neurotransmitters, chemicals, nutrition and the process of aging, can influence the adaptability of the muscle as a whole [1–4]. Specifically, the extent of mechanical loading appears to be an important factor in the plasticity of muscle fibres [5]. To study the effect of unloading or inactivation of muscles on the plasticity of muscle fibres, researchers have reduced mechanical loading using the hindlimb suspension model, bed rest and spaceflight [6–8].

Aging is another factor contributing to the plasticity of muscle fibres [9, 10]. Aging mainly has a negative effect on muscle fibres, both qualitatively and quantitatively, at the micro- and macro-levels. Indeed, the aging process can also contribute to unloading or inactivity of muscles. Several studies have addressed the moderating effects of the aging process on muscle plasticity, and these studies have focused on satellite cells, muscle fibres, fibre type transformation, adipocyte infiltration, mitochondria, myofilaments, E-C coupling and other possible factors [11, 12]. Moreover, muscle weakness and loss of muscle mass are important social issues among cohorts experiencing senescence [13]. Muscle atrophy because of aging leads to weakness, resulting in poor posture, impaired locomotion, decreased ability to perform daily activities and reduced quality of life [14].

One of the safest and most effective ways to delay and prevent the negative effects of aging and inactivity is physi-

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cal exercise. This review summarises the effects of exercise on single muscle fibre mechanics. In addition, it aims to interpret a huge range of information from both human and animal subjects, and describe how an exercise-oriented lifestyle can prevent muscular dysfunction.

The effect of aging on the mechanical properties of single muscle fibres

Sarcopenia occurs with aging and brings a decline in the functional, physiological and biochemical properties of muscles [15]. However, the question of whether the functional, physiological and biochemical declines observed on the macro-level are generally a result of micro-level phenomena is controversial. From the microscopic point of view, single muscle fibre analysis has been emphasised; however, previous studies have reported conflicting results. For example, Kim et al. reported functional declines (a decrease in Vo) in type II single muscle fibres with aging [16]. However, Korhonen et al. reported that human aged single muscle fibres did not show a difference in functional properties (Vo in type II fibres) (table 1) [17].

Another human study observed a change in mechanical properties in aged single muscle fibres compared with younger fibres [18, 19]; however, there were conflicting data reported in other studies [20, 21] (table 2). Krivickas et al. showed that the mechanical properties of muscle fibres from males and females with matched ages were distinctly different [29], and our recently published data also support this; we found significant difference ($p < 0.05$) between young men and young women in cross-sectional area and Vo (table 3) [9]. Together, these data suggest that many factors influence mechanical properties of muscle fibres, including experimental methods, the experimental environment, the species from which the fibres were derived, and subjects' characteristics (e.g., lifestyle, race and gender). Thus, more qualitative and quantitative studies should be conducted to define how these factors moderate the mechanical properties of muscle fibres.

There are also established factors that affect the mechanical properties of single muscle fibres: Ca^{2+} in the sarcoplasmic reticulum; the functionality of dihydropyridine and ryanodine receptors, which control the release of massive Ca^{2+} to induce the contraction of the muscle fibre [39]; the physiological state of multiple functional proteins such as titin, which function as templates or scaffolds on which the thick filaments could be assembled for muscle contraction [40]; the functionality of various proteins within the neuromuscular junction; the extent of degradation of muscle contractile proteins by aging, ATPase activity, and others, which affects muscular contractile malfunction [11].

Does exercise positively affect the mechanical properties of aged single muscle fibres?

In contrast to the controversies around the effects of aging on mechanical properties of muscle fibres (the decline in mechanical properties with aging [18, 19] vs no change in mechanical property [20, 21]), the effect of exercise on the mechanical properties of muscle is consistent. However, different types of exercise lead to differing results, and the results appear to be moderated by gender as such; Vo in type I fibres differ between young men and young women in our data (table 3).

One study reported that endurance exercise trains muscle endurance at the single muscle fibre level; however, it does not delay the atrophy of type II muscle fibres [41]. Endurance exercise enhances the capacity of the capillaries surrounding the fibres, but there are fewer capillaries surrounding the fibres in aged muscle [41–44].

Compared with endurance training, resistance training promotes greater gains in cross-sectional area (CSA, in μm^2) and Ca^{2+}-activated isometric force (Po = maximum contractile force, in mN). The difference between the type of training and the changes in mechanical properties of type I and type II single muscle fibres was greater in aged males than in younger counterparts [43, 45]. Twelve weeks of resistance training significantly increased muscle fibre size (16–24%) and force generating capacity (33–34%) in type I fibres of elderly women [46, 47]. In addition, aged male subjects who had been short-distance athletes (100 m running) showed a delayed reduction in type II fibre size and a slower shift in type I profile, contributing to greater fibre size, specific force (SF, in mN/mm^2), and explosive force production compared with normal, aged men [17]. Overall, exercise training-related studies showed that different types of loaded exercises had different effects on various fibre types; type I fibres showed a more effective and more sensitive adaptation response than other fibre types [48]. The adaption response in this fibre type is probably related with the sustainable and persistent mechanism orienting health maintenance.

Taken together, changes in the various muscle fibre types are dependent on the type of exercise. Interestingly, reports showed that exercise in the form of descending a mountain (inducing eccentric contractions) specifically recruited fast fibres [49, 50]. Compared with slow muscle fibre-specific physical activities, this form of fast fibre-specific training possibly builds fast fibre mass and functionality that contributes more effectively to fast fibre-derived force production. Thus, this training would be especially beneficial to the elderly population, who tend to lack fast fibre-derived force production, by maintaining or delaying the disappearing type II fibres in elderly people. Elderly people would then benefit from stronger muscles and fewer falls.

Table1: Shortening velocity of single muscle fibres between young and aged groups.

	Vo (FL/s)									
	IIa		IIa/x		IIx		IIx/b		IIb	
	Y	O	Y	O	Y	O	Y	O	Y	O
Kim et al. 2012 [16]	N/A	N/A	N/A	2.4 ± 0.3	2.7 ± 0.0	1.6 ± 0.3	3.2 ± 0.5	2.3 ± 0.2 *	3.3 ± 0.2	2.5 ± 0.2 *
Korhonen et al. 2006 [17]	1.8 ± 0.2	1.7 ± 0.1	2.4 ± 1.0	3.4 ± 0.6	4.2 ± 1.3	3.4 ± 0.8	N/A	N/A	N/A	N/A

O = old group; N/A = not applicable; Vo = maximum shortening velocity; Y = young group * indicates significant differences ($p < 0.05$) compared with the young group. Values are mean ± standard deviation.

Table 2: Summary of single muscle fibre studies of humans.

Investigators	Subjects (n, age)	Investigated muscle	Contractile properties			
			CSA (μm^2)	Po (mN)	SF (mN/mm^2)	CV (FL/s)
Power et al. 2016 [22]	Humans (n = 6, ~23 yr)	VL	8000 ± 2000	0.31 ± 0.06	41 ± 6	N/A
	Humans (n = 5, ~78 yr)	VL	6000 ± 1000	0.13 ± 0.02	23 ± 6	N/A
Reid et al. 2012 [23]	Men (n = 12, 40–55 yr)	VL healthy middle-aged (I)	5334 ± 1254	0.58 ± 0.14	165 ± 46	0.60 ± 0.20
		VL healthy middle-aged(IIa)	5354 ± 1411	0.48 ± 0.22	139 ± 65	1.33 ± 0.22
	Men (n = 16, 70–85 yr)	VL healthy old (I)	4999 ± 931	0.51 ± 0.08	154 ± 30	0.62 ± 0.13
		VL healthy old (IIa)	4902 ± 1500	0.43 ± 0.15	130 ± 38	1.54 ± 0.55
	Men (n = 12, 70–85 yr)	VL mobility limited (I)	4989 ± 1152	0.48 ± 0.14	147 ± 45	0.68 ± 0.20
		VL mobility limited (IIa)	4055 ± 794	0.33 ± 0.09	127 ± 38	1.59 ± 0.64
	Women (n = 11, 40–55 yr)	VL healthy middle-aged (I)	4880 ± 993	0.52 ± 0.13	158 ± 14	0.60 ± 0.10
		VL healthy middle-aged (IIa)	4016 ± 1312	0.41 ± 0.12	140 ± 21	1.29 ± 0.30
	Women (n = 7, 70–85 yr)	VL healthy old (I)	4407 ± 1174	0.45 ± 0.14	159 ± 41	0.65 ± 0.20
		VL healthy old (IIa)	4619 ± 949	0.46 ± 0.16	149 ± 63	1.36 ± 0.54
	Women (n = 13, 70–85 yr)	VL mobility limited (I)	4747 ± 887	0.48 ± 0.11	154 ± 36	0.62 ± 0.20
		VL mobility limited (IIa)	4110 ± 1646	0.39 ± 0.19	157 ± 83	1.24 ± 0.64
Hvid et al. 2011 [24]	Men (n = 9, ~24 yr)	VL Pre-immob. (I)	N/A	0.50 ± 0.03	81 ± 4	N/A
		VL Pre-immob. (IIa)	6458 ± 300	0.80 ± 0.05	119 ± 6	N/A
		VL Post-immob. (I)	N/A	0.40 ± 0.02	69 ± 4	N/A
		VL Post-immob. (IIa)	6215 ± 318	0.63 ± 0.05	97 ± 5	N/A
	Men (n = 8, ~67 yr)	VL Pre-immob. (I)	6922 ± 609	0.59 ± 0.04	77 ± 3	N/A
		VL Pre-immob. (IIa)	7587 ± 348	0.79 ± 0.08	117 ± 8	N/A
		VL Post-immob. (I)	6213 ± 576	0.45 ± 0.04	67 ± 4	N/A
		VL Post-immob. (IIa)	6626 ± 340	0.55 ± 0.07	88 ± 7	N/A
Hvid et al. 2010 [25]	Men (n = 11, ~24 yr)	VL Pre-immob. (I)	5180 ± 480	N/A	N/A	N/A
		VL Pre-immob. (IIa)	6073 ± 448	N/A	N/A	N/A
		VL Pre-immob. (IIx)	5458 ± 344	N/A	N/A	N/A
		VL Post-immob. (I)	4440 ± 500	N/A	N/A	N/A
		VL Post-immob. (IIa)	4537 ± 480	N/A	N/A	N/A
		VL Post-immob. (IIx)	3891 ± 441	N/A	N/A	N/A
		VL Training in post-immob. (I)	5386 ± 509	N/A	N/A	N/A
		VL Training in post-immob. (IIa)	6033 ± 534	N/A	N/A	N/A
		VL Training in post-immob. (IIx)	5558 ± 465	N/A	N/A	N/A
	Men (n = 9, ~67 yr)	VL Pre-immob. (I)	5301 ± 497	N/A	N/A	N/A
		VL Pre-immob. (IIa)	5029 ± 634	N/A	N/A	N/A
		VL Pre-immob. (IIx)	3715 ± 444	N/A	N/A	N/A
		VL Post-immob. (I)	4830 ± 587	N/A	N/A	N/A
		VL Post-immob. (IIa)	4269 ± 545	N/A	N/A	N/A
		VL Post-immob. (IIx)	2924 ± 200	N/A	N/A	N/A
		VL Training in post-immob. (I)	4848 ± 382	N/A	N/A	N/A
		VL Training in post-immob. (IIa)	4415 ± 371	N/A	N/A	N/A
		VL Training in post-immob. (IIx)	3542 ± 185	N/A	N/A	N/A
Raue et al. 2009 [26]	Young women (n = 9, ~21 yr)	VL (I)	4459 ± 382	0.51 ± 0.04	116 ± 8	0.90 ± 0.04
		VL (IIa)	3915 ± 427	0.61 ± 0.05	164 ± 12	3.13 ± 0.12
Slivka et al. 2008 [27]	Men (n = 6, ~82 yr)	VL Pre-training (I)	9300 ± 600	0.71 ± 0.09	102 ± 4	1.25 ± 0.06
		VL Pre-training (IIa)	8400 ± 600	0.88 ± 0.15	154 ± 10	3.19 ± 0.10
		VL Post-training (I)	8800 ± 800	0.64 ± 0.08	106 ± 6	1.40 ± 0.04
		VL Post-training (IIa)	8500 ± 700	0.87 ± 0.16	148 ± 6	3.40 ± 0.13
Trappe et al. 2008 [28]	Humans (n = 7, ~34 yr)	Soleus Pre-bedrest (I)	N/A	0.52 ± 0.03	81 ± 5	0.97 ± 0.06
		Soleus Pre-bedrest (IIa)	N/A	0.65 ± 0.03	123 ± 3	3.28 ± 0.31
		Soleus Post-bedrest (I)	N/A	0.32 ± 0.03	69 ± 4	0.90 ± 0.06
		Soleus Post-bedrest (IIa)	N/A	0.51 ± 0.06	121 ± 7	3.00 ± 0.37
Krivickas et al. 2006 [29]	Men (n = 6, 65–84 yr)	VL (I)	6040 ± 1585	0.56 ± 0.16	137 ± 41	0.69 ± 0.20
		VL (IIa)	4661 ± 1249	0.48 ± 0.14	146 ± 47	1.47 ± 0.49
	Women (n = 10, 65–84 yr)	VL (I)	5395 ± 1074	0.54 ± 0.12	149 ± 19	0.75 ± 0.18
		VL (IIa)	5109 ± 555	0.48 ± 0.07	143 ± 38	1.80 ± 0.29
Harber et al. 2004 [30]	Men (n = 8)	Gastroc. (I)	N/A	0.57 ± 0.08	72 ± 6	0.94 ± 0.17
		Gastroc. (IIa)	N/A	0.71 ± 0.09	90 ± 10	2.41 ± 0.55
D'antona et al. 2003 [31]	Immobilised, senescent (n = 2, 70 and 72 yr) 3 and 5months immo-bilised	VL (I)	N/A	N/A	189 ± 80	0.43 ± 0.39
		VL (IIa)	N/A	N/A	380 ± 317	1.42 ± 0.71
		VL (IIax)	N/A	N/A	292 ± 223	N/A

This fast fibre training would also ameliorate diabetes because fast fibres consume a glycolytic energy source and this training can enhance glucose disposal to the muscle [49, 51].

Mechanical properties of single muscle fibres in human and animals, and inactivity-derived mechanical properties of single muscle fibres

The plasticity of single muscle fibres is partly dependent on the isoform of myosin heavy chain. Heterogeneities of the myosin heavy chain isoform are associated with mechanical and physiological functionalities of muscles.

Table 2 provides an overview of previous studies, including the observed range of CSA, which is a morphological property that affects mechanical force. The ranges of CSA of human slow (type I) and fast (type IIa) muscle fibres were 4407–9300 and 3915–8500 μm^2, respectively. The corresponding Po values were 0.32–1.03 and 0.33–0.88 mN. The ranges of SF in human type I and type IIa fibres were 67–210 and 88–380 mN/mm^2, respectively. The contractile velocity of human type I and type IIa fibres were 0.35–1.42 FL/S and 1.07–3.40 FL/S, respectively. Even though the difference in size between slow and fast fibres is not significant, there is a large difference in Vo between slow and fast fibres.

Investigators	Subjects (n, age)	Investigated muscle	Contractile properties			
			CSA (μm^2)	Po (mN)	SF (mN/mm^2)	CV (FL/s)
		VL (I-IIax)	4057 ± 1285	N/A	228 ± 30	1.48 ± 0.85
		VL (I-II-neo)	3182 ± 527	N/A	176 ± 36	0.53 ± 0.51
Frontera et al. 2003 [32]	Young women (n = 7, ~26 yr)	VL (I)	4870 ± 930	0.55 ± 0.22	163 ± 40	N/A
Trappe et al. 2003 [20]	Human	VL young subjects (I)	6789 ± 364	N/A	94 ± 9	1.42 ± 0.13
		VL young subject (II)	6936 ± 442	N/A	122 ± 10	N/A
		VL elderly subjects (I)	8328 ± 565	N/A	93 ± 7	1.31 ± 0.10
		VL elderly subject (II)	6218 ± 419	N/A	133 ± 6	N/A
Widrick et al. 2003 [33]	Female, postmenopausal	VL (I)	5297 ± 193	0.61 ± 0.02	117.00 ± 2	0.61 ± 0.02
		VL (IIa)	4150 ± 231	0.59 ± 0.03	147 ± 4	2.80 ± 0.12
Krivickas et al. 2001 [34]	Young men (n = 7, ~36 yr)	VL (I)	N/A	N/A	N/A	0.77 ± 0.22
		VL (IIa)	N/A	N/A	N/A	2.14 ± 0.81
	Young women (n = 7, ~27 yr)	VL (I)	N/A	N/A	N/A	0.75 ± 0.20
		VL (IIa)	N/A	N/A	N/A	1.63 ± 0.37
Widrick et al. 2001 [35]	Men (n = 4)	Gastroc. (I) pre-spaceflight	N/A	0.68 ± 0.02	134 ± 2	0.60 ± 0.03
		Gastroc. (I) post-spaceflight	N/A	0.64 ± 0.02	133 ± 2	0.76 ± 0.02
		Gastroc. (IIa) pre-spaceflight	N/A	0.87 ± 0.03	151 ± 4	2.33 ± 0.25
		Gastroc. (IIa) post-spaceflight	N/A	0.83 ± 0.02	147 ± 3	3.10 ± 0.16
		Gastroc. (IIa/IIx) pre-spaceflight	N/A	0.84 ± 0.04	142 ± 5	3.85 ± 0.39
		Gastroc. (IIa/IIx) post-spaceflight	N/A	0.86 ± 0.04	149 ± 4	4.48 ± 0.33
Widrick et al. 1999 [36]	Young men (n = 4, ~42 yr)	Soleus (I)	N/A	1.03 ± 0.04	138 ± 4	0.69 ± 0.03
		Soleus (I) after 17 days spaceflight	N/A	0.91 ± 0.03	127 ± 4	0.80 ± 0.04
Widrick et al. 1997 [37]	Human men (n = 8, ~43 yr)	Soleus (I) Pre-bedrest	N/A	0.99 ± 0.02	139 ± 2	0.86 ± 0.02
		Soleus (I) Post-bedrest	N/A	0.86 ± 0.02	138 ± 3	1.15 ± 0.05
Larsson et al. 1993 [38]	Men and women (27–37yrs)	VL and soleus (I)	N/A	0.48 ± 0.13	210 ± 50	0.35 ± 0.16
		VL and soleus (IIa)	N/A	0.54 ± 0.18	200 ± 50	1.07 ± 0.37

CSA = cross sectional area; Gastroc. = gastrocnemius muscle; immob. = immobilization; N/A = not applicable; Po = maximum contractile force; SF (Po/CSA) = specific force; VL = vastus lateralis muscle; Vo = maximum shortening velocity Values are mean ± standard deviation.

Table3: Characteristics of human vastus lateralis single muscle fibres.

Classification	Fibre type	CSA (μm^2)	SF (mN/mm^2)	Vo (FL/s)	Po (mN)
YM	I (n = 65)	4679.69 ± 1143.48 *	125.64 ± 73.04	1.69 ± 1.19*	0.50 ± 0.41
	IIa (n = 27)	4779.22 ± 844.51	131.86 ± 67.16	2.25 ± 1.60	0.52 ± 0.37
	I/II hybrid (n = 19)	5202.21 ± 731.65	137.70 ± 66.19	2.77 ± 1.46	0.59 ± 0.35
OM	I (n = 21)	4503.95 ± 1769.54	123.34 ± 38.79	1.18 ± 0.93	0.45 ± 0.25
	IIa (n = 7)	3573.14 ± 1943.94	129.28 ± 114.56	1.84 ± 0.67	0.30 ± 0.20
	I/II hybrid (n = 6)	4962.83 ± 2574.96	138.64 ± 68.53	1.95 ± 1.12	0.59 ± 0.42
YW	I (n = 25)	4108.72 ± 103.17 *	116.99 ± 35.40	0.85 ± 0.35*	0.39 ± 0.16
	IIa (n = 4)	4436.50 ± 917.72	118.92 ± 75.58	0.99 ± 0.21	0.43 ± 0.28
	I/II hybrid (n = 2)	4001.50 ± 901.56	122.87 ± 32.76	0.62 ± 0.08	0.38 ± 0.01
OW	I (n = 31)	4050.13 ± 1072.37	104.53 ± 41.87	0.97 ± 0.42	0.34 ± 0.19
	IIa (n = 0)	N/D	N/D	N/D	N/D
	I/II hybrid (n = 5)	4656.80 ± 429.57	129.38 ± 70.47	1.99 ± 1.32	0.50 ± 0.30

CSA = cross-sectional area; N/D = not detected; OM = old men; OW= old women; Po = maximum contractile force; SF (Po/CSA) = specific force; Vo = maximum shortening velocity; YM = young men; YW = young women One-way repeated analysis of variance followed by the post hoc t-test was used for statistical significance. Values are means ± standard deviation. The entire experimental procedure was performed at 15.3 °C. * p <0.05: statistical significances between YM type I and YW type I (p = 0.021 for CSA and p = 0.016 for contractile velocity).

Table 4 shows the mechanical properties of muscle fibres measured in animal studies. CSA, Po, SF and contractile velocity for type I vs type IIa muscle fibres were 5558 vs 6120–7860 μm^2, 0.20–0.51 vs 0.24–0.94 mN, 52–113 vs 54–120 mN/mm^2, and 1.53–2.93 vs 2.97–5.63 FL/S, respectively (table 4).

Inactivity decreases muscle mass and fibre size, and consequently causes muscle weakness. It affects mechanical properties throughout the whole muscle level through alteration of the muscle pennation angle, fibre length, muscle size, tendons and other parts of the muscle. Morse and colleagues reported that inactivity-derived muscle atrophy with aging in the human gastrocnemius muscle showed reduced fibre size, SF and pennation angle, mainly related to reduced intrinsic muscle force [63].

Inactivity due to bed rest in a "load lessen" study corroborated the results described above. Bed rest of humans simulated the effect of inactivity on the hindlimb muscle in rats and led to a decrease in force, as well as an increase in type II fibre numbers and Vo in the soleus muscle. However, these phenomena were not seen in the gastrocnemius muscle, indicating a muscle-specific response. As shown

Table 4: Summary of single muscle fibre studies of animals.

Investigators	Subjects	Investigated muscle	Contractile properties			
			CSA (μm^2)	Po (mN)	SF (mN/mm^2)	CV (FL/s)
Kim et al. 2013 [6]	Rats (n = 5, 5–12 mo)	Medial gastroc. (I)	N/A	0.46 ± 0.02	113 ± 4	2.93 ± 0.20
		Medial gastroc. (II)	N/A	0.39 ± 0.02	100 ± 4	3.94 ± 0.21
	Rats (n = 7, 32–37 mo)	Medial gastroc. (I)	N/A	0.35 ± 0.02	95 ± 4	2.84 ± 0.20
		Medial gastroc. (II)	N/A	0.28 ± 0.01	86 ± 4	3.11 ± 0.18
Choi et al. 2012 [52]	Monkeys young female (n = 4, ~11 yr)	Vastus lateralis (IIa)	7860 ± 260	0.94 ± 0.03	120 ± 2	5.63 ± 0.26
	Monkey old female (n = 4, ~23 yr)	Vastus lateralis (IIa)	6120 ± 240	0.63 ± 0.03	102 ± 2	4.95 ± 0.22
Kim et al. 2012 [53]	Rats young (n = 8, 10–12 mo)	Semimembranosus (IIB)	N/A	0.76 ± 0.05	95 ± 4	3.30 ± 0.20
	Rats old (n = 8, 24–26 mo)	Semimembranosus (IIB)	N/A	0.42 ± 0.01	70 ± 2	2.50 ± 0.20
Kim et al. 2012 [54]	Rats (n = 16, 5–12 mo)	Soleus (I)	N/A	0.47 ± 0.01	95 ± 5	N/A
		Soleus (I) with hindlimb unloading (HU)	N/A	0.28 ± 0.01	91 ± 4	N/A
		Soleus (I) with HU + exercise	N/A	0.32 ± 0.01	77 ± 5	N/A
	Rats (n = 21, 32–40 mo)	Soleus (I)	N/A	0.42 ± 0.01	95 ± 5	N/A
		Soleus (I) with hindlimb unloading (HU)	N/A	0.25 ± 0.01	73 ± 4	N/A
		Soleus (I) with HU + exercise	N/A	0.20 ± 0.01	52 ± 4	N/A
Frontera et al. 2006 [55]	Rats female (n = 12, 228~252 g)	Tibialis anterior SCI 0 wk	4780 ± 1650	0.52 ± 0.22	164 ± 48	4.00 ± 1.00
		Tibialis anterior SCI 2 wk	4160 ± 1370	0.39 ± 0.18	141 ± 58	3.90 ± 1.20
		Tibialis anterior SCI 4 wk	6050 ± 1730	0.58 ± 0.19	141 ± 40	4.20 ± 1.20
Gonzalez et al. 2000 [56]	Mice young (n = 17 2~6 mo)	EDL	1187 ± 124	N/A	71 ± 13	N/A
		Soleus	1310 ± 100	N/A	48 ± 9	N/A
Lynch et al. 2000 [57]	Mice (n = 5, control compared with dystrophin transgene)	EDL	2326 ± 217	0.64 ± 0.05	270 ± 17	N/A
Thompson et al. 1999 [58]	Rats (n = 31, 12 mo)	Soleus (I)	5558 ± 222	0.51 ± 0.02	95 ± 5	1.71 ± 0.13
Sandmann et al. 1998 [59]	Rats (n = 18, 30 mo) Hindlimb (HU) Hindlimb + intermittent weight bearing (HUX)	Gastroc. (I)	N/A	0.39 ± 0.03	70 ± 5	1.19 ± 0.19
		Gastroc. (I-IIa)	N/A	0.38 ± 0.03	75 ± 5	2.31 ± 0.23
		Gastroc. (IIa)	N/A	0.41 ± 0.03	71 ± 5	3.46 ± 0.27
		Gastroc. (I) (HU)	N/A	0.26 ± 0.03	61 ± 6	1.53 ± 0.24
		Gastroc. (I-IIa) (HU)	N/A	0.25 ± 0.02	63 ± 6	3.54 ± 0.92
		Gastroc. (IIa) (HU)	N/A	0.24 ± 0.02	54 ± 5	3.72 ± 0.30
		Gastroc. (I) (HUX)	N/A	0.32 ± 0.03	59 ± 6	1.82 ± 0.28
		Gastroc. (I-IIa) (HUX)	N/A	0.28 ± 0.03	55 ± 6	2.98 ± 0.39
		Gastroc. (IIa) (HUX)	N/A	0.27 ± 0.03	56 ± 4	2.97 ± 0.29
Alley et al. 1997 [60]	Rats (n = 15, 30 mo)	Soleus	N/A	N/A	74 ± 21	0.98 ± 0.43
		Soleus 1 W hindlimb	N/A	N/A	56 ± 20	1.48 ± 0.75
		Soleus 1W hindlimb + intermittent weight bearing	N/A	N/A	66 ± 22	1.52 ± 1.11
Brook et al. 1988 [61]	Mice young (n = 11, 2–3 mo)	Soleus	1050 ± 60	0.21 ± 0.01	206 ± 67	4.8 ± 0.19
		EDL	1820 ± 60	0.41 ± 0.01	230 ± 80	10.4 ± 0.25
Herbert et al. 1988 [62]	Rat (n = 22, 250 g)	Soleus	N/A	N/A	N/A	1.05 ± 0.05
		Soleus with hindlimb	N/A	N/A	N/A	2.33 ± 0.06
		Soleus with hindlimb + exercise	N/A	N/A	N/A	2.33 ± 0.06

CSA = cross-sectional area; CV = contractile velocity; EDL = extensor digitorum longus muscle; gastroc. = gastrocnemius muscle; N/A = Not applicable; Po = maximum contractile force; SCI = spinal cord injury; SF (Po/CSA) = specific force; Vo = maximum shortening velocity; Values are mean ± standard deviation.

in table 4, Sandmann et al. reported that inactivity caused the specific force to decrease by 1.2–22% and Vo to increase by 7.5–29% in rat gastrocnemius muscle [64].

Alley and Thompson had similar results; 1 week of inactivity caused a 24% decrease in SF and a 51% increase in Vo in the hindlimb soleus muscle [60]. Moreover, Frontera and his colleagues showed that, after 2 weeks, the tibialis anterior muscle in spinal cord injury (SCI)-treated rats had a 14% decrease in SF; however, after 4 weeks the tibialis anterior muscle in SCI-treated rats did not further decrease in SF [55]. In the same study, SCI treatment for 2 weeks and 4 weeks caused a 2.5% decrease and a 5% increase, respectively, in Vo in the SCI-treated rats; however, there was no significant difference.

Another "lessen load" study in humans reported similar findings. Specifically, Widrick et al. reported that non-gravity spaceflight reduced SF in the soleus type I muscle by approximately 8% while increasing Vo by approximately 16% [33]. However, there is a muscle type-specific response: the gastrocnemius muscle tends not to respond to lessening gravity and decreased load. There are many hypotheses regarding these conflicting results from inactivity such as spaceflight, hindlimb suspension, or bedrest, but there is consensus that this inactivity / lessened load causes a decrease in specific force and an increase in Vo. The main cause is attributed to the loss of muscle mass and contractile muscle proteins.

Inactivity causes functional changes in the muscles. It initially induces functional changes in muscle, although the muscle maintains minimal functional capacity. Thus, the initial period of inactivity plays a crucial role in the loss of muscle function during the transition from activity to non-activity. However, those changes tend to preserve afferent activity, which is known to be fundamental for maintaining activation capacity after 2–4 weeks of steady inactivity [65].

In many inactivity-related phenomena with fibre type transitions, inactivity causes a non-common fibre shift. With aging, fast type II fibres degrade more rapidly and the balance of muscle fibre type shifts from fast to slow. On the other hand, an inactive vastus lateralis because of immobilisation, paralysis, bed rest, spaceflight, or hindlimb immobilisation shifts from slow to fast type fibres [66, 67].

The effects of inactivity on SF or fibre size depend on the length of the inactivity period. However, many studies unexpectedly showed that Vo increases over the period of inactivity. This unintuitive phenomenon is likely to be caused by reduced protein synthesis and selective loss of thin (actin) over thick (myosin) filaments [8].

Exercise during aging and inactivity causes positive changes in single muscle fibre properties

Exercise can combat muscular dysfunction caused by the aging process, neuromuscular damage, or other factors. Indeed, specific force declines with aging at a single muscle fibre level. A decline in specific force and muscle fibre deterioration are caused by many factors. For example, aging leads to changes in the attachments within the muscular-tendinous complex, leading to differences in mechanical force. Aging also leads to differences in functionally selected muscles, sometimes due to changes in posture or phasic function. There are also inherent changes that come with aging, including the sensitivity of Ca^{2+}, the activity of myofibrillar ATPase and temperature sensitivity [68, 69]. Finally, aging causes a decrease in the myosin head fraction in the strong binding structural state during muscle contraction at the micro-level [16]. This, in turn, leads to changes in actin and myosin composition, chemistry and, therefore, cross-bridge cycling [70–72]. These studies are in line with results from studies of participants with inactive lifestyles such as bedrest, demonstrating that inactivity can increase the risk of falling in aged persons. An interesting study reported that either weight bearing alone without workload or intermittent weight bearing can cause remarkable changes compared with regular activity at the level of the single muscle fibre; however, the change was muscle specific [64].

The greater the mechanical load imposed, the greater the effects. Various types of load-bearing exercises, including climbing with weight, chronic stretching and eccentric contractions, effectively reduce inactivity-related muscle atrophy.

In a study of mechanical properties of muscle in rats, Herbert et al. reported a 120% increase in Vo in the hindlimb soleus muscle with exercise (table 4). However, hindlimb immobilisation with exercise (rat climbing up a grid inclined at ~85% for eight repetitions with an added load of 75% of subject weight) did not affect the Vo of the soleus muscle [62].

There have also been studies that show benefits of exercise on muscle properties [73]. One year of resistance training caused a significant increase in SF and Vo in female subjects. The conflicting results suggest that differences in magnitude, duration, frequency, type and intensity of exercise, as well as different demographics of the participants, can affect the results. However, overall, therapeutic exercise is indispensable for maintaining muscle function and preventing atrophy.

Summary and evidence-based studies at the molecular level

In aging muscle, changes in mechanical properties at the single muscle fibre level generally depend on the fibre type. Type II fibres change to hybrid fibres and the proportion of type I fibres increases. Mechanical properties such as fibre size and specific force tend to decrease according to the loss of muscle mass owing to the loss of fibres (especially fast fibres). Various modalities of exercise change the physiological state, and changes in the mechanical properties of the muscle occur in order to maintain the evolving physiological state. This suggests that myosin heavy chain type I, not type II, might be influenced by the qualitative sensitivity of Ca^{2+} (cross-bridge cycling kinetics, Ca^{2+} binding site, and affinity of regulatory proteins for Ca^{2+}) [46]. Also, aging decreases sarcomere, myosin concentrations and the amount of thin filaments. Changes in these properties cause changes in the actin sliding velocity (Vo) in matched myosin isoforms [31].

Studies on neuromuscular activity related to inactivity showed that changes in the quality and quantity of actin and myosin cross-bridges, E-C coupling, denaturation of dihydropyridine and ryanodine receptors within the sarcoplasmic reticulum, and other factors can contribute to

muscle adaptability. A decline in muscle function was associated with a change in the binding structure of the myosin heavy chain head, thus thwarting binding with actin molecules.

Perkins and colleagues reported factors influencing the mechanical properties of muscles [74]. They noted that certain structural modifications in myosin molecules, nitration [58], and oxidisation of cysteine residues in the myosin molecule not involved in catalysis of myosin ATPase activity, affect muscle properties. Canepari et al., in an *in-vitro* study, supported these results and showed that modification of myosin molecules affected the Vo of an isolated muscle fibre, and the magnitude of the effect depended on the muscle fibre types that housed the myosin molecule [21].

In conclusion, mechanisms to maintain or improve muscular functionality have been identified. Results from these studies can help ameliorate contractile dysfunction and prevent atrophy caused by the aging process and inactivity. To prevent muscular dysfunction and minimise muscle atrophy, an exercise-oriented lifestyle is recommended.

Disclosure statement

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