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Myofascial Force Transmission via Extramuscular Pathways Occurs between Antagonistic Muscles

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Key Words
Anterior crural compartment · Anterior tibial muscle · Connective tissue · Extensor digitorum longus muscle · Extensor hallucis longus muscle · Length-force characteristics · Myofascial force transmission · Peroneal compartment · Proximo-distal force difference · Rat model

Abstract
Most often muscles (as organs) are viewed as independent actuators. To test if this is true for antagonistic muscles, force was measured simultaneously at: (1) the proximal and distal tendons of the extensor digitorum muscle (EDL) to quantify any proximo-distal force differences, as an indicator of myofascial force transmission, (2) at the distal tendons of the whole antagonistic peroneal muscle group (PER) to test if effects of EDL length changes are present and (3) at the proximal end of the tibia to test if myofascially transmitted force is exerted there. EDL length was manipulated either at the proximal or distal tendons. This way equal EDL lengths are attained at two different positions of the muscle with respect to the tibia and antagonistic muscles. Despite its relatively small size, lengthening of the EDL changed forces exerted on the tibia and forces exerted by its antagonistic muscle group. Apart from its extramuscular myofascial connections, EDL has no connections to either the tibia or these antagonistic muscles. Proximal EDL lengthening increased distal muscular forces (active PER $\Delta F \approx +1.7\%$), but decreased tibial forces (passive from 0.3 to 0 N; active $\Delta F \approx -5\%$). Therefore, it is concluded that these antagonistic muscles do not act independently, because of myofascial force transmission between them. Such a decrease in tibial force indicates release of pre-strained connections. Distal EDL lengthening had opposite effects (tripling passive force exerted on tibia; active PER force $\Delta F \approx -3.6\%$). It is concluded that the length and relative position of the EDL is a co-determinant of pas-

Abbreviations used in this paper

Δl_{m+t}	the change of muscle-tendon complex length of muscle or complex of muscles
EDL	m. extensor digitorum longus (with tied distal tendons)
EHL	m. extensor hallucis longus
FCU	m. flexor carpi ulnaris
F_{ma}	active force exerted by a muscle, or muscle complex
F_{mao}	optimal force
F_{mp}	passive force exerted by a muscle, or muscle complex
l_{mao}	optimum length
PER	complex consisting of the peroneal muscle group (i.e. m. peroneus longus, m. peroneus brevis, m. peroneus quarti and m. peroneus quinti), with tied distal tendons
TA + EHL	complex consisting of m. tibialis anterior and m. extensor hallucis longus, with tied distal tendons

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sive and active force exerted at tendons of nearby antagonistic muscle groups. These results necessitate a new view of the locomotor apparatus, which needs to take into account the high interdependence of muscles and muscle fibres as force generators, as well as proximo-distal force differences and serial and parallel distributions of sarcomere lengths that are consequences of such interaction. If this is done properly, the effects of integrating a muscle fibre, muscle or muscle group into higher levels of organisation of the body will be evident.

Introduction

The length of muscular elements is generally recognized as one of the major determinants of force exerted. As a consequence, for more than a century, isometric length-force characteristics have been the subject of extensive research. Such experimental work involved whole muscle isolated except for its blood supply [Rack and Westbury, 1969; Bobbert et al., 1990; Gareis et al., 1992], isolated small muscle fascicles [Street, 1983; Zuurbier et al., 1995; Willems and Purslow, 1997; Zuurbier et al., 1998] and single muscle fibres [Ramsey and Street, 1940; Gordon et al., 1966; ter Keurs et al., 1978; Julian and Morgan, 1981; Willems and Purslow, 1997]. Even work on force transmission from muscle fibres focussed on muscles that are mechanically isolated from its surroundings. This was studied within either non-spanning fibred muscle [Loeb et al., 1987; Purslow and Duance, 1990; Eldred et al., 1993; Purslow and Trotter, 1994; Roy et al., 1995; Trotter et al., 1995; Brown et al., 1998; Purslow, 2002] or within muscles consisting of fibres that span the distance between its proximal and distal aponeurosis [Huijing et al., 1998].

Such approaches are the result of considering generally such muscular elements as independent actuators until fairly recently. After pioneering physiological work [Street and Ramsey, 1965], the growing knowledge of molecular connections [Berthier and Blaineau, 1997; Spence et al., 2002] between intra- and extracellular structures at many locations on the periphery of a cell, combined with a growing general interest in the collagen fibre-reinforced extracellular matrix and its functional effects has contributed to, and sometimes implicitly challenges, the concept of mechanical independence of muscle fibres [Loeb et al., 1987; Purslow and Duance, 1990; Eldred et al., 1993; Purslow and Trotter, 1994; Roy et al., 1995; Trotter et al., 1995; Brown et al., 1998; Boriek et al., 2001; Purslow, 2002] and fascicles [Huijing et al., 1998], but also of muscles [Huijing, 1999a].

If muscles were mechanically independent actuators, force exerted at its origin and insertion would be equal. In the last few years, we showed that this is mostly not the case: Proximo-distal force differences exist [Huijing, 1999b; Huijing and Baan, 2001; Maas et al., 2001], as long as the muscle is working within its connective tissue context. Interaction effects for synergistic muscles within one compartment by epimuscular myofascial force transmission were shown in the same studies. Not for all muscles measuring force at origin and insertion is experimentally feasible; therefore, alternative methods to ascertain if epimuscular myofascial force transmission occurs are necessary.

Mechanical interaction effects due to myofascial force transmission were hypothesized recently for antagonistic muscles [Huijing, 2003], since the direction of length change is opposite and, therefore, their relative position is changed most drastically of all muscles during any joint movement.

In view of the above, the major aims of the present work are to test the following null hypotheses. (1) Active and passive forces exerted by EDL on the tibia will be zero, because its tendons are not attached to it. (2) The change in force exerted by antagonistic peroneal muscles kept at constant length will not significantly deviate from zero, on changing the length of rat EDL. (3) After EDL is lengthened to identical muscle-tendon complex lengths by displacing either its proximal or distal tendons, the change in its proximo-distal force difference, as well as the change in force exerted by antagonistic muscles does not deviate significantly from zero.

Materials and Methods

Male Wistar rats (n = 6, mean ± SD of body mass 293 ± 12.73 g) were used in the experiment. Surgical and experimental procedures were in compliance with the guidelines and regulations concerning animal welfare and experimentation set forth by the Dutch law and were approved by a Committee on Ethics of Animal Experimentation at the Vrije Universiteit, Amsterdam.

Immediately after all experiments, double-sided pneumothorax was performed and animals were killed with an overdose of pentobarbital.

Surgery and Experimental Procedures

Details of surgical and experimental procedures are presented in Appendix 1.

In summary, the anterior crural and peroneal compartments were left intact.

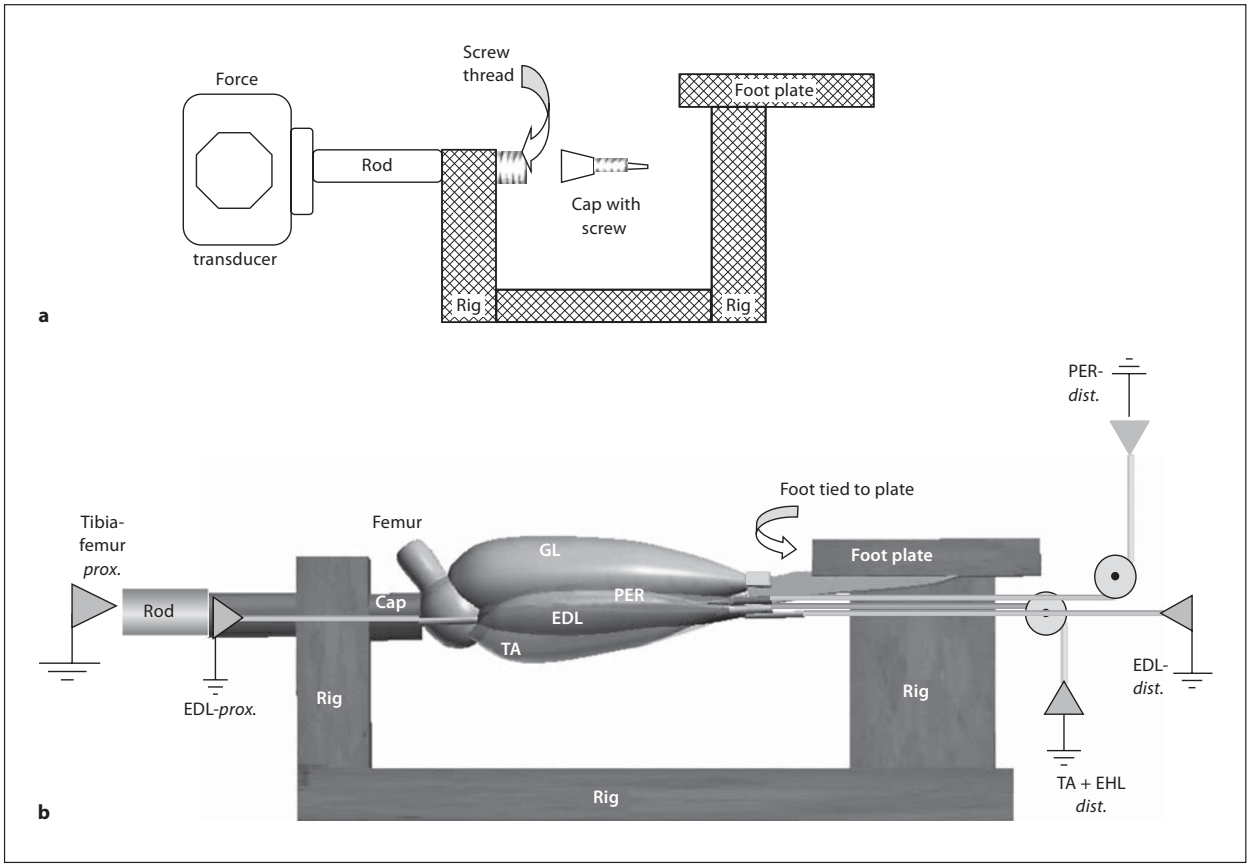

Fig. 1. Schematic representation of the experimental set-up. **a** The rig used for mounting the cut femur, tibia and foot. Nearby, the rat is placed on a plateau (not shown). The animal provides circulation of blood through the preparation. A screw is inserted into a hole drilled through the femur and knee joint into the tibial plateau and glued and fastened. Holding this screw is a cap, which is screwed onto a rod. The rod is attached to a force transducer measuring the force exerted of the tibia-femur complex. This force transducer supports the whole experimental rig with the leg. **b** After mounting the animal with the rig in the set-up, the foot is tied to the foot plate to make room for passage of Kevlar threads attached to distal tendons. Subsequently the muscle and muscle complexes are attached to force transducers, either directly (EDL) or via low friction pulleys. The latter is the case for the TA + EHL and the PER complexes. The EDL belly is mostly hidden below the TA, but is made visible in this image by making the TA transparent. GL = m. gastrocnemius caput lateralis; prox. = proximal; dist. = distal. The triangles represent the force transducers used.

The following structures were connected to force transducers (fig. 1): EDL tendons (proximal as well as distal); (2) tied distal tendons of tibialis anterior (TA) and extensor hallucis muscles (EHL); (3) tied distal tendons of peroneal muscles, and (4) the complex of femur and tibia. The sciatic nerve was cut from the central nervous system and used for supramaximal electrical stimulation. The blood circulation in the lower leg and foot was left intact.

Experimental Protocol

For the experimental protocol applied, three phases can be distinguished which were performed in the following order.

Initial Contractions to Minimize Effects of Previous Activity at High Length. Specific care had been taken that experimental muscles did not attain high length before this part of the experiment. Isometric tetanic EDL force was measured at a test length (i.e. a length at which approximately 0.5 N of active distal force was exerted) with simultaneous measurements of force of the TA + EHL complex, while at constant complex length. Subsequently, EDL was brought to high muscle-tendon complex length (i.e. approximately 1 mm over optimum length) and activated isometrically. After the recovery period near active slack length, EDL was brought again to the test length and activated. Due to the previous activity at high length, force at the test length was decreased substantially without changing optimal force [Huijing and Baan,

2001]. Therefore, the procedure described was repeated (approximately 4–5 times) until the previous activity at high length did no longer change the force exerted at the test length.

Distal Lengthening for Determination of EDL Length-Force Characteristics. EDL muscle-tendon complex length changes were imposed first by moving the distal force transducer (1-mm increments, determined on a vernier mechanism read to the nearest tenth of a mm) prior to contractions. Proximal tendons were kept at reference position. Length-force data were obtained starting from active slack length and ending approximately 2 mm over optimum length.

Proximal Lengthening for the Determination of EDL Length-Force Characteristics. Subsequently, EDL muscle-tendon complex length changes were imposed by moving the distal force transducer (1-mm increments, determined on a vernier mechanism read to the nearest tenth of a mm) in between contractions. Distal EDL tendons were kept at reference position. Length-force data were obtained starting from active slack length and ending approximately 2 mm over optimum length.

Force Measurement System

In order to make sure that any differences in force transducers and their calibration prior to the experiment introduced no artefact, the two force transducers to be used for measurement of EDL forces were connected to each other using a compliant spring. The output was recorded with the same measurement system (i.e. amplifiers, A/D converters) used in the animal experiment. It is concluded that any major difference in force (>1.36%) at these transducers cannot be ascribed to the measurement system used. In addition to that, the locations of these proximal and distal force transducers for EDL were exchanged in half of the experiments.

Data Processing

The individual EDL length-force data sets for passive muscle force and muscle length were fitted with an exponential curve (equation 1), using a least squares criterion.

$$y = e^{a_1 + a_2 \cdot x} \quad (1)$$

where y represents passive muscle force, x represents passive muscle-tendon complex length (i.e. deviation from minimal length: Δl) and a_1 and a_2 are coefficients determined in the fitting process. Active muscle force (F_{ma}) was estimated by subtracting passive force calculated according to equation 1 for the appropriate active muscle-tendon complex length from the total force exerted by the muscle at that length.

Data for active EDL force (F_{ma}) in relation to active muscle-tendon complex length (Δl) were fitted using a polynomial:

$$y = b_0 + b_1 \cdot x + b_2 \cdot x^2 + \ldots + b_n \cdot x^n \quad (2)$$

where y represents active muscle force F_{ma}, x represents length of the active muscle-tendon complex, n represents the order of the polynomial, and b_0, b_1, b_2 ... b_n are coefficients determined in the least square fitting process. The fitting started with a first order polynomial and the power was increased up to and including the sixth order. Polynomials that best described the experimental data were selected. These polynomials were used for three purposes: determining (1) EDL optimal force and (2) optimum length, and (3) averaging of data and calculation of standard errors. For each individual muscle, optimal muscle force (F_{mao}) is defined as the maximum of the fitted polynomial for active muscle force, and optimum muscle-tendon complex length is defined as the corresponding active length.

Similar fitting procedures were used for fitting the data relating passive as well as active force to EDL length for the muscle complexes that were kept at constant lengths, and also for passive and active proximal tibial force.

Individual data for EDL muscle-tendon complex lengths were expressed as deviations from EDL length attained in the reference position (corresponding to the length with knee at 105° and ankle at 90°).

Statistics

In the fitting procedure, one-way analysis of variance (ANOVA) [Neter et al., 1990] was used to select the lowest order of the polynomials that still added a significant improvement in the description of changes of muscle-tendon complex length and muscle force data for EDL.

Two-way ANOVA for repeated measurements (factors: EDL muscle-tendon complex length and either location of EDL lengthening or location of EDL force measurement) was performed to test for effects on EDL length-force characteristics measured simultaneously. The same procedure (factors EDL muscle tendon-complex length and location of EDL lengthening) was applied also on data regarding (1) distal force exerted by the TA + EHL muscle complex, (2) distal force exerted by the PER muscle complex kept at constant length, and (3) distally exerted EDL force as well as (4) proximally exerted force by the tibia to test for differential effects of proximal and distal lengthening.

If any significant effects were found, post-hoc tests were performed using the Bonferroni procedure for multiple paired comparisons, to further locate significant differences.

To test for any differences in proximal and distal optimum length as well as forces exerted at reference length and position, or to test further for length effects, one-way ANOVA for repeated measurements was performed.

Any differences at $p \leq 0.05$ were considered significant.

Results

Evidence for Epimuscular Myofascial Force Transmission for EDL

Differences between Proximal and Distal EDL Forces

EDL forces exerted at its proximal and distal tendons (fig. 2) are almost never equal (ANOVA showed significant effects of length and location of lengthening, as well as a significant interaction between these factors for both active and passive forces). This is indicative for paths of force transmission alternative to myotendinous transmission.

The magnitude of this proximo-distal force difference is quite dependent on EDL muscle-tendon complex length. For example for distal lengthening, between zero and maximally 43% of the active force exerted at the dis-

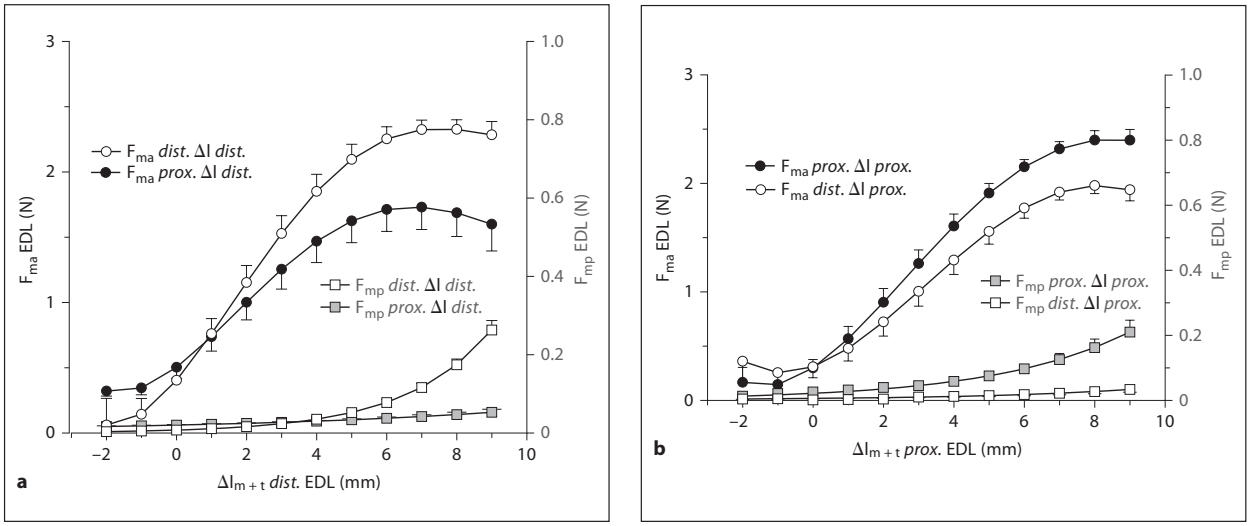

Fig. 2. Length-force characteristics of rat EDL for proximal (prox.) and distal (dist.) lengthening. **a** Distal lengthening of the muscle-tendon complex. **b** Proximal lengthening of the muscle-tendon complex. Active (F_{ma}) as well as passive (F_{mp}) forces exerted at proximal as well as distal EDL tendons are shown (means and SE). EDL length is indicated as deviation (Δl_{m+t}) from its length in the reference position, i.e. with the knee joint at 105° and the ankle joint at 90°. Note that data are plotted in **a** and **b** for equal lengths, but that the force values differ substantially.

tal tendon at the highest length is not exerted at the proximal tendon. Lengthening to the identical EDL length by displacement of proximal end yields quite a different result: 19% of the active force exerted at the proximal tendon is not exerted at the distal tendon. Note that the sign of the force difference (i.e. the direction of the net myofascial force transmission) depends if the muscle was lengthened by displacing its proximal or distal end (compare fig. 2a and b). Note that the length at which the change in direction transmission of active force occurs is not identical for proximal and distal EDL lengthening (c.f. fig. 2a and b: difference approximately 1 mm).

Manipulating EDL Length Affects Force Exerted on the Tibia

In the present experiment, EDL has neither an origin nor insertion on the tibia itself or on lower limb parts still connected to the tibia. Nevertheless, force exerted on the tibia is a function of EDL muscle-tendon complex length (fig. 3). For active forces exerted on the tibia, ANOVA showed significant effects of location of EDL lengthening, as well as interaction between factors EDL length and location of lengthening. For example, after distal EDL lengthening, active forces on the tibia were increased (fig. 3a) by peak $\Delta F \approx 0.5$ N or 7% initial force). Passive force exerted on the tibia increased much more (fig. 3b: by peak $\Delta F = 0.12$ N, i.e. almost tripling the initial force!). Note also that lengthening of EDL at its distal tendon has an opposite effect on force exerted on the tibia (fig. 3a: active $\Delta F = -0.38$ N, i.e. $\approx -5\%$ of initial active force; fig. 3b: on EDL lengthening passive force exerted on the tibia decreases from $F \approx 0.32$ N to approximately 0).

Effects of EDL Length and Relative Position on Force Exerted by Antagonistic Muscles Kept at Constant Length

EDL is located within the anterior crural compartment and the peroneal muscle group (PER) within the peroneal compartment. The content of these compartments are separated by the anterior intermuscular septum.

For active PER force (fig. 4a), ANOVA showed significant effects for the factor location of EDL lengthening, as well as interaction between the factors EDL length and location of EDL lengthening. Note that this effect is dependent on the location lengthening of EDL: (a) lengthening of EDL by displacing its distal tendon decreases active force measured at the PER distal tendons ($\Delta F \approx -3.6\%$) and (b) displacing the EDL proximal tendon increases this force ($\Delta F \approx +1.7\%$). For passive PER force (fig. 4b), ANOVA showed significant effects for factor location of EDL lengthening.

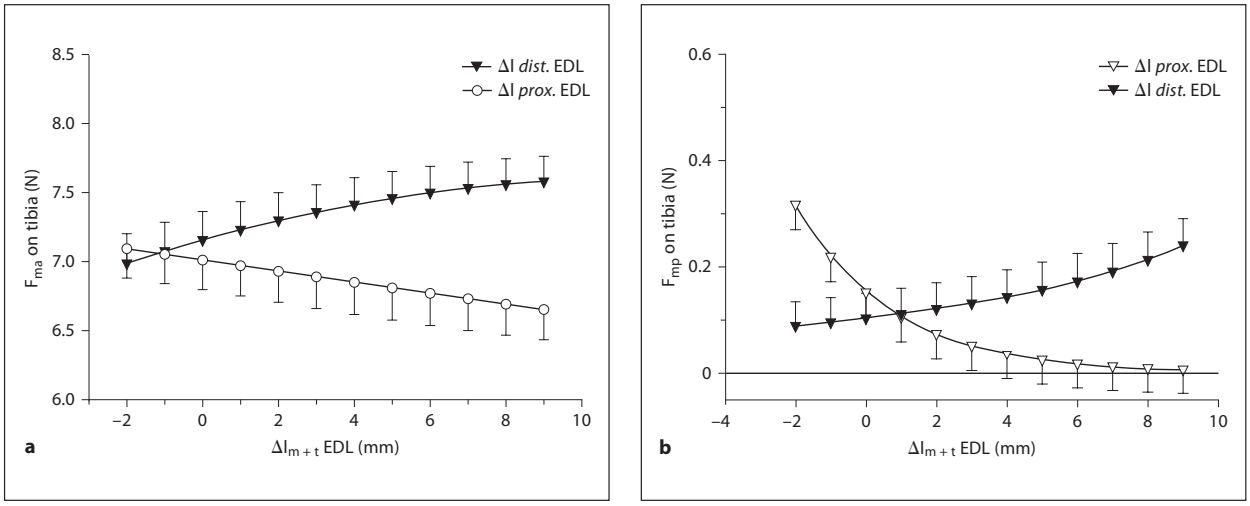

Fig. 3. Effects of proximally (prox.) and distally (dist.) changing EDL length on forces exerted on the tibia-femur complex. **a** Active forces. **b** Passive forces. Tibia force is shown as means (SE). EDL muscle-tendon complex length is indicated as deviation (Δl_{m+t}) from its length in the reference position, i.e. with the knee joint at 105° and the ankle joint at 90°. Note that EDL has no myotendinous connections to the tibia or to tissues directly connected to the tibia. Note also that distal and proximal lengthening of the EDL muscle-tendon complex yield quite different results.

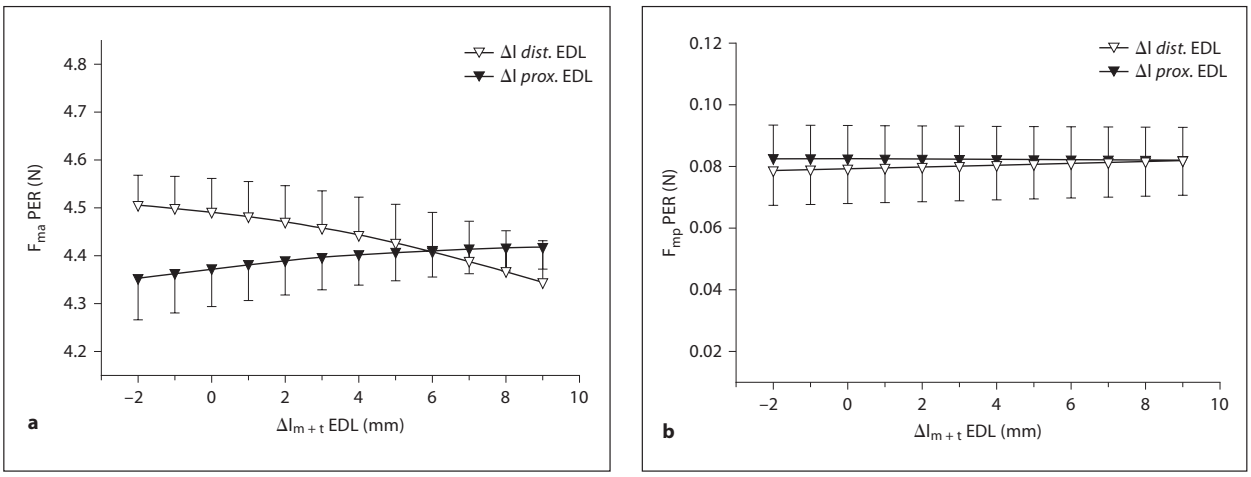

Fig. 4. Effects of proximally (prox.) and distally (dist.) changing EDL length on forces exerted by the antagonistic PER kept at constant length. **a** Active forces. **b** Passive forces. Distal PER active and passive forces are shown as means (SE). EDL length is indicated as deviation (Δl_{m+t}) from its length in the reference position, i.e. with the knee joint at 105° and the ankle joint at 90°. Note that EDL has no myotendinous connections to the PER or to tissues directly connected to this muscle complex.

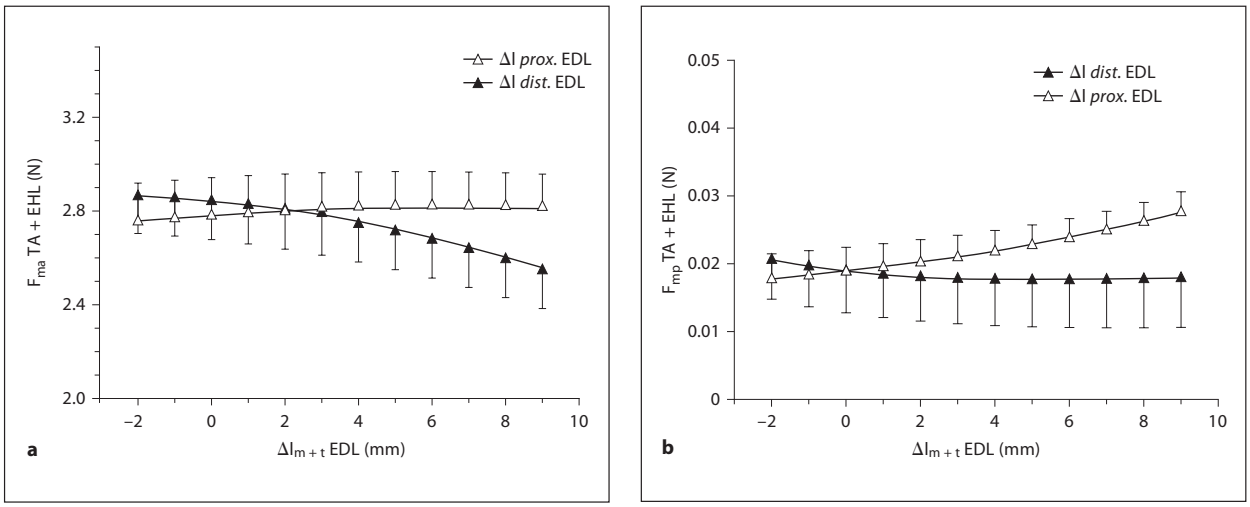

Fig. 5. Effects of proximally and distally changing EDL length on forces exerted by the synergistic TA+EHL muscle complex kept at constant length. **a** Active forces. **b** Passive forces. Distal TA+EHL active and passive forces are shown as mean and standard error. EDL length is indicated as deviation (Δl_{m+t}) from its length in the reference position, i.e. with the knee joint at 105° and the ankle joint at 90°. Note that EDL has no myotendinous connections to the TA+EHL or to tissues directly connected to this muscle complex.

For the sake of completeness, results for TA + EHL are shown in figure 5. Note that results are qualitatively similar as for PER (fig. 4), i.e. decreasing force on distal EDL lengthening, increasing force on proximal EDL lengthening. However, the effects are more enhanced for synergistic interaction.

Discussion

The present results can be summarized as follows: The length-dependent EDL proximo-distal force differences indicate myofascial force transmission between EDL and its surrounding tissues. The change in sign of the EDL proximo-distal active force difference (fig. 2) indicates that the direction of myofascial force transmission changes as a function of EDL length. In addition, this direction is dependent on the location of EDL lengthening.

Fractions of force, transmitted myofascially from or onto EDL, are exerted: (1) on the tibia-femur complex to which the EDL is not connected other than by myofascial connections, and (2) on the antagonistic muscle group PER. The former constitutes novel evidence for epimuscular myofascial force transmission as well as for effects of changes of the relative position of muscle with respect to its surroundings on such force transmission. The latter leads to the conclusion that even a relatively big muscle group as the peroneal group is not fully independent of the length and relative position of much smaller antagonistic EDL, because of myofascial force transmission.

Our novel observations of decreasing tibial force with increasing EDL length (fig. 3) provides experimental support for the notion that myofascial connections may be pre-strained [Yucesoy et al., 2005]. Interactions between adjacent synergistic muscles within the anterior crural compartment have been observed previously [Yucesoy et al., 2001; Huijing and Baan, 2003; Maas et al., 2003b; Yucesoy et al., 2005] and in the present work (not shown). The present work also reconfirms previous results [Huijing, 1999a] on the asymmetry of effects of proximal and distal EDL lengthening. A novel aspect of our present results is that such asymmetric effects occur also for neighbouring antagonistic muscles.

The collagen fibre reinforcement of blood vessels and nerves (referred to as neurovascular tract) seems most important for linking synergistic muscles mechanically [Maas et al., 2006]. The common peroneal nerve and some blood vessels and their collagen fibre reinforcement pass between the peroneal and anterior crural compartments through a fenestra (fig. 6) within the septum. This structure may thus play an important role in intercompart-

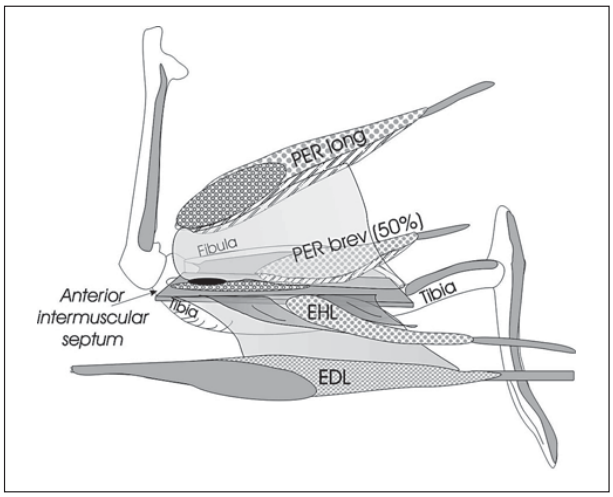

Fig. 6. Schematic lateral view of anterior crural and peroneal muscles. The view is semi-exploded to reveal connections of the neurovascular tracts within their compartments to muscles and compartmental connective tissues. The femur, tibia and fibula are shown directly and/or through transparent structures indicating the neurovascular tracts that are collagen fibre reinforcements of blood vessels and nerves. The two compartments are separated by the anterior intermuscular septum indicated by a grey solid plane. Note that in physiological conditions the neurovascular tracts have a form much closer to cables, sometimes at best with small membrane-like extensions as connection to the septum. The black spot on the septum indicates the fenestra through which major blood vessels and nerves pass between the compartments. The m. tibialis anterior has been removed. For the peroneal compartment, only the most laterally located peroneal muscles are shown: mm. peroneus longus (PER long) and brevis (PER brev, (50%) indicates only half of this muscle shown). Active and passive force being transmitted between the antagonistic muscles (see fig. 4) is hypothesised to follow the paths of the sheared neurovascular tracts. Part of that force is exerted at the tibia (via the interosseal membrane). Note that figure 3 indicates that some of these paths may be under substantial pre-tension in most conditions.

mental force transmission. On both sides of the septum, the neurovascular tracts are attached over their full lengths at the interface of the septum and interosseal membrane (fig. 6). However, other extramuscular structures such as periost and the compartmental fascia may contribute to the stiffness of transmission paths. Force exerted via such pathways may contribute to moments exerted at joints, e.g. even after dissection of the triceps surae compartment, active force originating from sarcomeres within plantaris muscle was exerted via epitendinous tissues at the calcaneus [Rijkelijkhuizen et al., 2005].

Sources of Error and Limitations of the Study

The length at which the change of direction of transmission of active force occurs is not identical for proximal and distal EDL lengthening (c.f. fig. 2a and b: difference approximately 1 mm). This means that we have not been fully successful in totally removing effect of previous activity at high length and that the results for proximal lengthening also contain small length history effects. However, this does not affect major features of the present result.

Of course, the conditions of our experiments differ from in vivo conditions. It should be noted that the present work reports results for muscles that are active maximally. Recent observations indicate that the fraction of muscle forces that is transmitted myofascially between synergistic muscles via epimuscular pathways is enhanced in sub-maximally activated muscle [Meijer et al., 2006]. The relative importance of such transmission, compared to myotendinous force transmission, increases with decreasing activation.

Another major deviation of our experiment from in vivo conditions is that only the length of one muscle-tendon complex is changed (in casu EDL), while that length of neighbouring synergistic and antagonistic muscles is kept constant. The experiment was designed this way to be able to show unequivocally the myofascial interaction effects between antagonistic muscles. In vivo, cramp or spastic shortening in one muscle or movement of only one head of a muscle resembles that condition, but usually limb movement will involve simultaneous length changes of many muscles. It should be noted for synergistic muscles that for limb movement the changes in relative position of synergistic muscles will be smaller than in our experiments, but sometimes such effects will still be notable; e.g. for mice, mean moment arm at the ankle of TA muscle is 17% higher than of EDL [Lieber, 1997]. For human muscles, from data of changes of muscle-tendon complex length of quadriceps muscle heads [Visser et al., 1990], we derive that maximal changes in muscular relative position during full knee flexion movement may amount to approximately 10% of femur length (i.e. many cm). During limb movement, changes in relative position of agonistic muscles will be bigger than in our experiment (the agonist shorten and antagonistic muscles lengthen simultaneously). Co-activation of synergists and antagonists is a common feature of in vivo movement in health [van der Wal, 1988; Kellis et al., 2003; Croce et al., 2004; Kingma et al., 2004; Kubo et al., 2004; Maltais et al., 2004] and disease [Berger et al., 1982, 1984; Dietz et al., 1995; Segawa, 1995; Thomas et al., 1998; Levin et

al., 2000; Pousson et al., 2001; Maltais et al., 2004]. On the basis of these arguments, we expect that myofascial force transmission between antagonistic muscles will be enhanced during limb movement, even if levels of recruitment are considerably lower than in our present study.

Epimuscular Myofascial Force Transmission Is a General Phenomenon for Different Species as well as Different Locations within the Body

In the rat, evidence for epimuscular myofascial force transmission was shown also for flexor carpi ulnaris muscle located within the lower front leg [Smeulders et al., 2002]. It is also expected that myofascial force transmission between antagonistic muscles of more comparable size will be quantitatively more important [a preliminary result is reviewed by Huijing and Jaspers, 2005]. Such pilot work indicates that distal lengthening of the whole rat anterior crural muscle group decreases distal force exerted by the peroneal muscle group by approximately 30%. It was also found for human arm and leg muscles (see Appendix 2). Therefore, we conclude that myofascial effects are not very location-specific.

Viewed across species, epimuscular myofascial force transmission also seems a rather general phenomenon, as evidence is available for rats [see also Huijing and Baan, 2001; Maas et al., 2003a; Yucesoy et al., 2003a, b; Maas et al., 2004], mice [Meijer et al., 2007a], amphibians [a preliminary result published in Huijing and Jaspers, 2005], chicken [Bender, 2003] and locust [Meijer et al., 2007b]. In this context, the observations on flight muscle in locusts are striking, because of the completely different anatomical organisation of the limbs of insects.

Some Functional Implications of Myofascial Force Transmission between Muscles

The implicit or explicit opinion is often encountered that animal and human movement may be best explained if muscles are considered as independent units of force generation and even that humans need independent actuators to be able to accomplish the wide range of varied and sometimes intricate motions. The present work shows that mechanisms of force transmission are active that make muscles less independent of each other and of non-muscular tissues surrounding them than expected. In contrast to such opinions, we present an opposite vision that the intricate movements that humans and other animals perform are only possible because of the complex interactions indicated above. Rather than needing a specific muscle for each specific movement, prevention of movement and joint stabilization tasks to be performed, the needed effects can be obtained by manipulating the degree of excitation, lengths and relative positions of the whole set of muscles within the context of the collagen-reinforced extracellular matrix of the whole limb or whole body.

We have argued previously [Huijing, 2003; Huijing and Jaspers, 2005] that characteristics (e.g. length force curves, but also long-term adaptive responses to altered conditions) of muscular entities (cells, tissue and organs, but also muscle groups) will be changed on integration into a higher level of organization. These changes are brought about by interaction between muscular entities and between non-muscular and muscular structures via the connective tissue that forms the integrative stroma of the higher order of organization. We expect that such mechanical interactions are not limited to muscular units, but may occur for other cell-tissue-organ systems as well, but we will limit the discussion to the muscular system.

Force Transmission and Signal Transduction in Adaptation

That epimuscular myofascial force transmission will not only have consequences for the acute mechanical properties of a muscle, but also for processes of adaptation, may be illustrated by the following example: Adaptation of serial number of sarcomeres within muscle fibres and atrophy or hypertrophy that have been shown to occur commonly for muscles during in vivo immobilization at lengths deviating from optimum length [Tabary et al., 1972, 1976; Tardieu et al., 1977; Tabary et al., 1981] were not found as an isolated muscle fibre (with intact basal lamina-endomysium complex) is kept at similar lengths during long-term culture [Jaspers et al., 2001, 2002, 2004, 2006]. It seems likely that mechanical interaction between muscle fibres and their collagen-reinforced extracellular matrix plays a major role in adaptive responses, either by affecting the cytoskeleton directly (mechano-transduction) or by changing stimulation of receptor molecules at the sarcolemma (chemo-transduction). It is important to realize that such cell-matrix interaction is affected by the conditions of the target muscle and its surrounding synergistic muscles and extramuscular connective tissues. Our present results indicate that even the mechanical conditions of antagonistic muscles may play a role in such processes. It is conceivable that the enhanced serial distribution of sarcomere length within muscle fibres due to epimuscular myofascial force transmission plays an important role in adaptive processes.

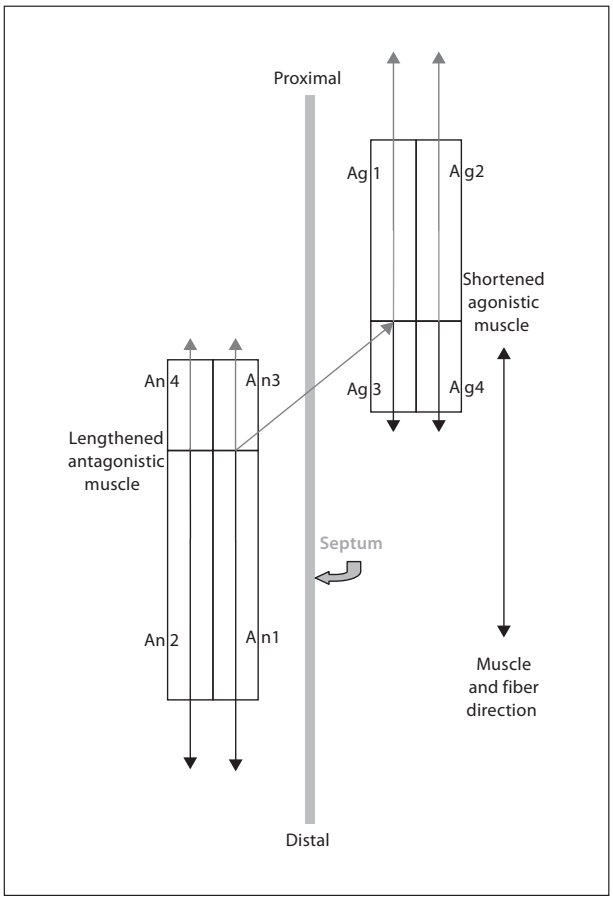

Fig. 7. Schematic representation of connections between antagonistic muscles and their effects of extramuscular myofascial force transmission. For a particular movement, a shortened agonistic muscle (right) and its nearby lengthened antagonistic counterpart (left) is shown. The muscles are separated by an intermuscular septum (thick grey line), and two muscle fascicles arranged in parallel within each of the muscles are indicated. Black or grey arrows indicate muscle force and reaction forces, respectively. The net epimuscular load imposed by the extramuscular connections on the agonistic muscle is assumed to affect the two fascicles equally. The point of application is drawn at horizontal lines separating two populations of sarcomeres within each muscle. This additional load prevents the proximal sarcomeres within the fibres of the agonistic muscle (i.e. Ag1 and Ag2) to shorten any further than drawn. This means that most of the muscle shortening is caused by the distal sarcomere populations (i.e. Ag3 and Ag4). As a consequence a serial distribution of sarcomere lengths is present within the muscle fibres of the agonistic muscle. The additional myofascial force is transmitted by the extramuscular connections (through the septum) onto the antagonistic muscle and is integrated in the forces exerted by its distally located collagen-reinforced extracellular matrix-muscle fibres complexes (i.e. An1 and An2). To bear the myofascial force, in addition to the myotendinous force the sarcomeres have to be long. This means that most of the lengthening of the antagonistic muscle originated from its distal parts. In contrast, the proximal complexes (i.e. An3 and An4) only bear myotendinous forces and are shorter. Also in the antagonistic muscles, a serial distribution of sarcomere lengths is present. Note that the distal elements of the antagonistic muscle are arranged in series with the proximal elements from the agonistic muscles and can also be considered a functional unit that actually has less serial distribution of sarcomere length than the fibres of either of the muscles.

Distributions of Sarcomere Lengths

Figure 7 shows the simplest schematic representation possible of force transmission between antagonistic muscles. The additional force, exerted on muscle via intercompartmental myofascial force transmission, will lead to enhanced distributions of sarcomere lengths. At one end of the muscle fibre, a group of serial sarcomeres will be short (those not exposed to the epimuscular myofascial force, see fig. 7, Ag3–4 and An3–4) and at the other end sarcomeres will be longer (those exposed to that load, see fig. 7, Ag1–2 and An1–2). Enhanced distribution of sarcomere length will lead to enhanced length range of active force exertion [Willems and Huijing, 1994].

Recommendations and Topics for Future Work

A most important step to take into account the described effects of myofascial connections between muscles and between muscles and non-muscular tissues is to refrain from considering muscles and muscle fibres as rather homogeneous and independent units of force exertion.

This is particularly true for biomechanical modeling of muscles active within an in vivo context. This means that the most simple Hill-type models (representing the muscle as one sarcomere in which all modeled characteristics are lumped, are not adequate for studying effects for non-isolated muscle. Conceivably, several of such classical models should be placed in series to allow major effects of myofascial force transmission. It is also true for the anatomical sciences, for which a new approach is needed. Most activity in dissection effectively removes the myofascial connections. In view of the concept of epimuscular myofascial force transmission, a new type of dissection is needed, which is aimed at exposing the connections. It is interesting to note that in the history of anatomy, basic elements of such a type of dissection were

performed [e.g. the examples of cross-sectional anatomy within the different volumes of the atlas of Bourgery et al., 1866–1871], but have become unusual, to say the least, in modern days.

If such dissection is performed on living tissues of experimental animals, experiments may be designed to test the material and structure properties of the connections, and how these mechanical properties are affected as the structures are integrated in a higher order of organisation. In addition, the modern non-invasive imaging techniques (ultrasound, MRI) and 3D reconstruction may assist to visualize and understand the in vivo characteristics of such connecting structures. Despite the lack of information regarding muscular forces exerted, such studies can significantly contribute to morphological and strain aspects.

An additional approach to enhance the understanding of functional effects of myofascial force transmission is to interfere with it and study the effects of such interventions. The most simple way of doing that is progressive dissection (only a simple start with such experiments has been made [Huijing et al., 2003; Maas et al., 2006]).

Alternatively and probably more interesting, because of its additional information regarding muscle fibre and fibrocyte pathologies, is the study of myofascial force transmission in experimental animals, in which parts of the tentative molecular pathways are removed or altered by naturally occurring deficiencies in pathway molecules or by experimental molecular intervention [Lopez et al., 2005]. However, such work is also needed for a muscle active within its natural context of connective tissue to evaluate myofascial force transmission aspects on interaction between muscles. Work is needed at all levels of organisation, however, in addition, integrative effects of higher levels of organisation should also be taken into account.

In sum, mechanisms for significant mechanical interaction between antagonistic muscles by myofascial force transmission are shown to cause interdependence of force exerted at proximal and distal tendons of such muscles. Even changing the length and relative position of a relatively small muscle (EDL) does affect force exertion of the much bigger peroneal muscle group, located nearby, but across from the intermuscular septum. Lengthening of EDL also affects forces exerted via extramuscular connective tissues within the two compartments. Such demonstration of inter-antagonistic myofascial force transmission invites the creation of a new view of the human and animal locomotor apparatus, which needs to take into account the very limited independence of muscles and muscle fibres as force generators, the proximo-distal force differences, and serial and parallel distributions of sarcomere lengths which are consequences of such interaction.

In addition to the levels of organisation referred to in the title of this Journal (cell, tissue and organ), higher levels have to be considered as well (limb or whole body) to be fully able to account for the effects described in the present work.

Appendix 1: Details of Experimental Methods

Surgical Procedure and Preparation for the Experiment

The animals were anaesthetized by intra-peritoneal injection of a urethane solution (initial dose 150 mg/100 g body mass). Supplementary doses of the anaesthetic agent (0.62 mg) were injected intra-peritoneally (maximally 3 times) if necessary to maintain deep anaesthesia. The animals were placed on a heated water pad (37°C) during surgery.

Femoral Compartment

The left femoral compartments were opened and manipulated intensively in order to:

(1) Cut the sciatic nerve as proximally as possible. The sural, tibial and articular branches of the sciatic nerve were cut, so that by stimulating the sciatic nerve during the experiment, only the muscles innervated by the common peroneal nerve would be activated exclusively.

(2) Cut and remove all upper leg muscles with the exception of the m. abductor brevis and m. caudo-femoralis, which were left intact to help protect the blood vessels to the lower leg that pass along their surfaces.

(3) Cut the femur transversely to allow later fixation within the experimental set-up.

(4) Free the insertion of the proximal tendon of EDL.

(5) With knee at 105° (full extension corresponding to 180°) drill a small hole through the femur between the condyles and through the knee joint into the tibial plateau. Fill the whole with tissue glue (Histoacryl) and insert a self-tapping screw (material: electrolytic zinc-plated steel, diameter: 2 mm). The screw head was restrained by an aluminium cap with thread on its inside, for later use for attachment of the femur and its rig to the force transducer (fig. 1).

Anterior Crural Compartment

In the rat, for the biceps femoris muscle to reach its extended insertion along the tibia, connective tissue associated with this muscle covers the anterior compartment. Removing the skin, parts of the crural fascia and the biceps femoris muscle exposed the anterior crural compartment of the left leg. The very distal part of the anterior tibial compartment had to be opened (local fasciotomy) to reach the distal tendons of EDL and of the EHL and TA muscles. With the knee joint at approximately 105° and the angle between the footplate and the tibia at 90° (referred to as reference positions), two sets of distal tendons were tied together: (1) the four adjacent distal tendons of EDL (using polyester thread) and (2) the distal EHL tendon was tied to the adjacent distal tendon of TA (using polyester thread). The complex of TA and EHL created this way will further be referred to as TA + EHL.

Matching markers were placed on the distal tendons of EDL and of TA and EHL, as well as on a fixed location on the lower leg.

Peroneal Compartment

The peroneal compartment was opened only distally to reach the distal tendons of the peroneal muscle group (PER). This group of four peroneal muscles (i.e. mm. peroneus longus, peroneus brevis, peroneus quarti and peroneus quinti, respectively), fill most of the compartment. Their distal tendons were dissected free from surrounding tissues, leaving the compartmental borders and connective tissues around the muscle bellies fully intact. The four adjacent distal peroneal tendons were tied together using polyester and Kevlar threads.

Further Treatment of the Tendons of Target Muscles

The retinaculae at the ankle (i.e. transverse crural ligament and the cruciate ligament) were removed, while under observation through a dissection microscope (Wild, magnification ×6–50). Subsequently, tenotomy was performed as distally as possible on the distal EDL and TA + EHL, as well as PER tendon complexes. The severed tendons were removed from their retinaculae near the ankle joint (transverse crural ligament and cruciate ligament). The proximal tendon of EDL was cut loose from the femur, with a small piece of the lateral femur condyle still attached.

Using polyester threads, each of the distal tendon complexes as well as the proximal EDL tendon were sutured to Kevlar threads with a small loop at their end (proximal or distal, respectively). Subsequently, the left foot of the rat was attached firmly to an aluminum footplate using a Kevlar thread. If necessary the tendons were irrigated with an isotonic saline solution to prevent drying. All Kevlar threads used (Goodfellow, Great Britain) were 0.5 mm in diameter and characterized by a 3.7% elongation at breaking. All polyester threads used (Gütermann, Germany) had a diameter of 0.3 mm.

Mounting the Animal in the Experimental Apparatus

The body of the rat was put on a supporting table with a warm water supply (temperature 37°C). The cap, holding the knee-tibial screw, was screwed onto a stiff aluminium rod (diameter 8 mm). This rod was attached to a force transducer (for a schematic view see fig. 1a). The force transducer supports the whole rig containing the experimental leg. The foot plate was manipulated to make room for passage of distal tendon complexes and their attached Kevlar threads (fig. 1b). Subsequently, the footplate was fixed to the experimental rig (with the ankle joint in extreme plantar flexion and approximately 40° of supination).

Experimental Procedure

During the experiments, ambient temperature was kept constant at 22 ± 0.5°C and air humidity was kept at 80 ± 2% by a computer-controlled air conditioning system (Holland Heating) creating a down flow of air onto the experimental table. The surfaces of the compartments were rinsed regularly with saline to prevent fluid loss.

TA + EHL and EDL muscles (innervated via the deep peroneal nerve) but also the whole peroneal muscle group (innervated by the superficial peroneal nerve) were excited simultaneously. This was done by stimulating the distal end of the severed sciatic nerve placed on a bipolar stimulation electrode connected to a constant current source (square pulse width 100 μs, pulse train 400 ms, 100 Hz). Stimulation current of the nerve was set at supramaximal levels. In the preparatory phase of each experiment, current was increased in small steps until no further increase in force was attained. In this condition, currents of approximately 3 mA were necessary. The constant current mode of the stimulator delivers the set amplitude of current, even if changes of nerve impedance should occur during the experiment, thereby helping to maintain maximal excitation of the nerve during the course of the experiment. To prevent drying of the nerve, the exposed part was covered with paper tissue, saturated with isotonic saline, which itself was covered by a thin layer of latex.

The TA + EHL complex was brought to a muscle-tendon complex length corresponding initially to a summed distal active force of approximately 3 N. Subsequently, the peroneal muscles were set a muscle-tendon complex length corresponding to a summed distal active force of approximately 5 N. Such setting of muscle-tendon complex lengths as defined by force exerted has been shown to yield reproducible settings. The EDL distal tendon group was set at a position corresponding approximately to reference position.

All four Kevlar threads attached to tendons were connected to force transducers (Hottinger Baldwin; maximal output error <0.1%, compliance 0.0048 mm/N). For proximal EDL as well as TA + EHL and the peroneal complex, the Kevlar wires were guided over low friction pulleys, which were shown not to affect force measurements prior to the experiments.

The 3-D co-ordinates of the force transducers were manipulated to obtain orthogonal orientations with respect to the Kevlar threads.

After lengthening of EDL muscle to any desired target length, two twitches were evoked (200 ms apart). Passive force was determined at approximately t = 580 ms. During the tetanic plateau (i.e. 275 ms after evoking tetanic stimulation), total isometric muscle force was determined. All force signals were acquired using an A/D converter (sample frequency 1,000 Hz, resolution of force 0.01 N) and recorded on a microcomputer. A special purpose microcomputer controlled timing of events related to stimulus generation as well as A/D conversion.

Following each isometric contraction, the muscles were allowed to recover for 2 min. For EDL, recovery was allowed to occur near active slack length (i.e. the lowest length at which active muscle force approaches zero). The positions of distal tendons of the TA + EHL complex as well as the peroneal complex were kept constant throughout the experiment. As the origins of these muscles were not treated in any way, the muscle-tendon complex length of these muscle groups were constant during experiments.

Appendix 2: Myofascial Force Transmission in Humans

Also in humans, indications have been found for myofascial force transmission if experimental conditions can be controlled well enough. For human rectus femoris muscle after recovery from a distal tendon transposition to a flexor position, Delp and co-workers reported effects [Riewald and Delp, 1996; Asakawa et al., 2002, 2004, 2006] that can only be fully understood if epi-

muscular myofascial force transmission is taken into account: Despite distal tendon transfer to a flexion insertion, the rectus femoris muscle exerts an extensor moment at the knee. Due to the tendon transfer, the rectus femoris muscle has become antagonistic in function to the other heads of m. quadriceps, but is still myofascially intimately connected to them, with its connections evidently enabling exertion of an extensor force at the knee.

Also in humans, experiments similar to our experimental animal experiments were performed during surgery on arm muscles of patients suffering from spastic paresis [Kreulen et al., 2003; Smeulders et al., 2004a, b]. The most simple indication for epimuscular myofascial force transmission in humans was found during such surgery: After tenotomy of the flexor carpi ulnaris muscle (FCU), as the wrist was dorsally flexed by the surgeon, active and passive FCU was lengthened, despite the fact that the FCU tendon no longer crossed the wrist that was moved [Kreulen et al., 2003]. In fact, after tenotomy but before dissection, such lengthening of the FCU was 89% of the value before tenotomy. This can only happen if synergistic muscles or other structures that are lengthened by wrist dorsal flexion or antagonistic muscles that are shortened by that movement manage to exert a force in distal direction on FCU. Dissection of all connective tissues around the FCU for approximately one third of its full length (minimally necessary for FCU tendon transfer to a dorsal flexor location) decimates, but does not fully remove the effect (7.2% of initial lengthening remains).

On the basis of the above considerations, we expect potentially important functional consequences of synergistic and antagonistic interaction by myofascial force transmission to be widespread over species.

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