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Perspective Article

Hylonome

What is new in musculoskeletal interactions? Lateral force transmission, botox, calcium and bone strength, and osteocyte apoptosis

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Muscular adaptations to resistance training: the case for lateral force transmission

An increase in force of human skeletal muscle following resistance training is generally ascribed to changes in muscle mass and architecture, and in neural activation capacity.

While these phenomena have been extensively studied in the past, a number of methodological limitations precluded an exhaustive examination of the relationships between the increase in strength and other training-induced adaptations. By using latest technology for the assessment of muscle structure and function, Erskine et al.[1] circumvented these limitations and delivered one of the most comprehensive estimations of *in vivo* muscular adaptations to heavy resistance training. By combining measurements of isometric torque, agonist (interpolated twitch technique) and antagonist (electromyography) neural activation, muscle architecture (ultrasound), muscle volume and patellar tendon moment arm (magnetic resonance imaging), the authors estimated the specific tension of the whole quadriceps muscle, calculated as the ratio of the patellar tendon force by the summated physiological cross section areas of each head of the quadriceps. Importantly, apart from muscle volume, all measurements were obtained near optimum sarcomeric length, during maximal voluntary contraction at a knee joint angle enabling maximal torque production. One might - rightly - argue that despite this unprecedented level of complexity for a training study, the validity of the outcome is not perfect, for most of these variables still rely on necessary assumptions/approximations. Nevertheless, the findings from this study are surprising: an increase in quadriceps specific tension, largely independent from changes in neural factors. The authors quote a number of possible factors to explain their results, including changes in myofilaments packing density, increase in the proportion of type IIX fibres, or the possible role of lateral force transmission. An elevation of force per cross sectional area of single muscle fibres and a shift in fibre-type composition towards type IIX have indeed both been reported in the extreme case of bodybuilders, following years of heavy resistance loading[2]. However, such adaptations are unlikely in young humans subjected to short term resistance training[3], leaving the controversial hypothesis of lateral force transmission.

The concept of lateral force transmission is not new (see[4] for review). According to this theory, in addition to force transmitted longitudinally along the fibres, force is also transmitted laterally between the contractile units of adjacent muscle fibres via costameres and the extracellular matrix. Thus, the force output measured at the whole-muscle level is the sum of these two forces from within the muscle. Experimental evidence from elegant animal studies using fibre dissection[5] and tenotomy[6] techniques supports this theory. More recently, Huijing and colleagues have also reported interesting data suggesting myofascial force transmission from the muscle to its surroundings (reviewed in[7]), although the notion of epimuscular lateral force transmission is still debated[8]. Structural analyses substantiate the fact that intramuscular connective tissue is indeed able to transmit forces: the organisation of endomysial collagen fibrils indicates that shear forces may be transmitted between overlapping tapered myofibres[9]. Similarly, scanning electron microscopy revealed that the architecture of bovine perimysium enables lateral force transmission[10]. Despite this circumstantial evidence, lateral force transmission is difficult to demonstrate *in vivo* and its potential impact on tendon force transmission is not universally accepted. This scepticism and technical difficulties have limited the investigation of this phenomenon in the previous years, and a training-induced enhancement of lateral force transmission has hitherto never been reported.

The adaptive response of the extracellular matrix to mechan-

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ical loading and notably the increase in collagen synthesis is relatively well documented[11]. Some authors have observed that this increase is linked to the increase in myofibrillar protein synthesis occurring after a bout of resistive exercise[12]. Part of this timely increase in collagen synthesis is probably directed towards the remodelling of muscle fibres and fascicles, to accommodate new contractile material. Another part of it, however, probably serves other purposes such as stress shielding or, possibly, lateral force transmission. In support of this, recent findings by Holm et al.[13] indicate that training-induced production of collagen synthesis is not necessarily linked to an increase in myofibrillar content. In this study, the authors used an intra-subject design to investigate the influence of exercise intensity and feeding on collagen and myofibrillar fractional synthesis rate. It was found that collagen synthesis increases after a low-intensity bout of resistive exercise, while myofibrillar synthesis does not. Moreover, the magnitude of the post-exercise elevation in collagen fractional synthesis rate was not affected by contractile intensity. The functional purpose of newly synthesised collagen deposition cannot be drawn from that study, but previous literature suggests that following high intensity, lengthening, muscle contractions, an increase in type IV collagen is directed towards remodelling of the basement membrane of myofibres[14]. Interestingly, however, the magnitude of collagen protein synthesis seems similar after lengthening and - less disruptive - concentric muscle contractions[15].

The fact that the exercise-induced increase in muscular collagen synthesis occurs with low intensity contractions and with relative independence of myofibrillar synthesis and contraction type suggests that the purpose of connective tissue remodelling is not restricted to the accommodation of muscular hypertrophy or to maintain structural integrity of the muscle fibre. Despite the numerous methodological obstacles to an accurate assessment of *in vivo* muscular adaptations to training in humans, the discrepancies between the estimated changes in muscle force and the extent of muscular hypertrophy may be underpinned by unexplored mechanisms of force increase. Future animal studies may elucidate whether these mechanisms include lateral force transmission, by combining measurements of muscular collagen metabolism with the design of previous studies demonstrating non-myotendinous force transmission.

Oxidative stress in old muscles

As all our life ultimately relies upon oxidative metabolism, there is a need to balance the throughput of oxygen and the formation of free radicals. This ambiguous business seems to become increasingly difficult at old age. How that ambiguity relates to exercise is illustrated by a recent study by Hollander et al.[16]. As demonstrated in rat, stretch-shortening contractions, i.e. a combination of eccentric and concentric muscle contractions, can increase intra-muscular levels of glutathione in old, but not in young animals. This group difference was maintained even during pharmacological inhibition of glutathione synthesis. One would conclude, accordingly, that stretch-shortening exercise could be particular beneficial at old age. Unfortunately, lipid peroxidation, i.e. a marker of oxidative damage likewise was increased by stretch-shortening contractions in the old animals only, reversing the aforementioned notion. And what is even more, a subsequent study failed to demonstrate an aggravation of the age-related deterioration in response to stretch shortening exercise by glutathione depletion[17], which begs the question whether glutathione, or oxidative stress altogether, is the crucial mechanism of muscular senescence.

Of wrinkles and research

Further progress has also been made on the botox (= botulinum toxin) front. Whilst plastic surgeons use this compound to combat wrinkles, clever researchers are nowadays wrinkling outdated scientific ideas with it. Botox has no known direct effect on bone cells, but inhibits synaptic transmission in skeletal muscle and thus leads to flaccid paralysis. Accordingly, its injection in to a muscle leads to the muscle's atrophy and induces bone loss[18-19]. What really makes this interesting is the fact that the response is local and limited in time. Now, such temporal changes, including their recovery, have been studied in more detail than before[20]. Quite interestingly, trabecular bone loss from the proximal tibia epiphysis preceded cortical bone losses, indicating different speeds of adaptation within the bone. However, whilst recovery of cortical bone losses from the shaft was good, trabecular losses from the metaphysis recovered only poorly during the 84 days follow-up. In particular was there no recovery of trabecular number, suggesting that it is difficult, if not impossible to structurally restore the trabecular network once it has been disrupted. This might also be the reason why bone losses induced by experimental bed rest do recover in the cortex of the distal tibia epiphysis, but not in the trabecular portion of that anatomical site[21]. Coming back to our botox story[20], it is of note that trabecular bone loss appeared to be even faster than loss in muscle volume. Other authors, by contrast, have reported that changes in muscle and bone depict a very similar time course[22]. Quite interestingly, and despite that they depart from contrasting observations, both teams of authors suggest the same conclusion, namely that muscle function will be more important than muscle volume as a governing signal for bone.

When too much calcium is bad for bone

Although hypercalcaemia is an alarming medical disorder, most doctors would agree that calcium is generally good – at least for bone. In what appears to be a Sysiphean labour, Busse et al. now devastate this simplistic view, namely when it comes to mechanical competence of single trabeculi[23]. When comparing equally sized isolated rod-like trabeculi from young, non-osteoporotic women with those obtained from old, osteoporotic women it turned out that fracture load was reduced by 10% and work to failure by 35% in the ostoporotic samples, highlighting the prerogative to consider material properties when discussing osteoporotic fractures. Moreover, calcium content was greater in osteoporotic than in non-osteoporotic

samples. The actual difference was astoundingly small (4%), and the more striking feature was the pronounced inhomogeneity of the calcium distribution. The physiological reason behind this could well be an accumulation of calcium-rich cement lines that comes with age. Although it will be a challenging task to demonstrate a causative relationship between increased calcium-content and mechanical incompetence, this study clearly shows that whatever the true cause might be, calcium cannot help it.

Osteocyte apoptosis and remodelling

Talking about bone losses and their prevention, let us turn to a key agent that is receiving increasing attention. From when it was first proposed that osteocyte apoptosis is linked to bone resorption[30], more and more evidence has been accumulated in support of this conjecture. We have known since, for example, that osteocyte apoptosis can help to target the remodelling process[31], that disuse-mode remodelling is turned on by osteocyte apoptosis[32], and that estrogen can prevent osteocyte apoptosis by an antioxidant effect[33]. What was not exactly known was whether and how osteocyte apoptaosis is involved in ovariectomy-induced bone loss – a gap that now has been filled by Mitch Schaffler's group[34]. What the authors demonstrate in their beautiful piece of research is that osteocyte apoptosis precedes endocortical resorption in a strict topological relationship within the femur of ovariectimized mice. Moreover, a supposedly osteocyte-selective apoptosis inhibitor was demonstrated to specifically inhibit this bone loss. The obvious question is now how the apoptotic osteocyte can activate or attract the cells of the osteoclast lineage. And, of course, the jury is now hung for the development of osteocyte-selective apoptosis inhibitors. These could prove to be a major step, as osteocyte vitality turns out to be vital to ourselves.

References

1. Erskine RM, Jones DA, Williams AG, Stewart CE, Degens H. Resistance training increases *in vivo* quadriceps femoris muscle specific tension in young men. Acta Physiol (Oxf) 2010;199:83-9.
2. D'Antona G, Lanfranconi F, Pellegrino MA, Brocca L, Adami R, Rossi R, Moro G, Miotti D, Canepari M, Bottinelli R. Skeletal muscle hypertrophy and structure and function of skeletal muscle fibres in male body builders. J Physiol 2006;570:611.
3. Adams GR, Hather BM, Baldwin KM, Dudley GA. Skeletal muscle myosin heavy chain composition and resistance training. J Appl Physiol 1993;74:911-5.
4. Huijing PA. Muscle as a collagen fiber reinforced composite: a review of force transmission in muscle and whole limb. J Biomech 1999;32:329-45.
5. Street SF. Lateral transmission of tension in frog myofibers: a myofibrillar network and transverse cytoskeletal connections are possible transmitters. J Cell Physiol 1983;114:346-64.
6. Huijing PA, Baan GC, Rebel GT. Non-myotendinous force transmission in rat extensor digitorum longus muscle. J Exp Biol 1998;201:683-91.
7. Huijing PA. Epimuscular myofascial force transmission between antagonistic and synergistic muscles can explain movement limitation in spastic paresis. J Electromyogr Kinesiol 2007;17:708-24.
8. Maas H, Sandercock TG. Are skeletal muscles independent actuators? Force transmission from soleus muscle in the cat. J Appl Physiol 2008;104:1557-67.
9. Trotter JA, Purslow PP. Functional morphology of the endomysium in series fibered muscles. J Morphol 1992; 212:109-22.
10. Passerieux E, Rossignol R, Letellier T, Delage JP. Physical continuity of the perimysium from myofibers to tendons: involvement in lateral force transmission in skeletal muscle. J Struct Biol 2007;159:19-28.
11. Kjaer M. Role of extracellular matrix in adaptation of tendon and skeletal muscle to mechanical loading. Physiol Rev 2004;84:649-98.
12. Miller BF, Olesen JL, Hansen M, Dossing S, Crameri RM, Welling RJ, Langberg H, Flyvbjerg A, Kjaer M, Babraj JA, Smith K, Rennie MJ. Coordinated collagen and muscle protein synthesis in human patella tendon and quadriceps muscle after exercise. J Physiol 2005; 567:1021-33.
13. Holm L, Hall GV, Rose AJ, Miller BF, Doessing S, Richter EA, Kjaer M. Contraction intensity and feeding affect collagen and myofibrillar protein synthesis rates differently in human skeletal muscle. Am J Physiol Endocrinol Metab 2009.
14. Mackey AL, Donnelly AE, Turpeenniemi-Hujanen T, Roper HP. Skeletal muscle collagen content in humans after high-force eccentric contractions. J Appl Physiol 2004;97:197-203.
15. Moore DR, Phillips SM, Babraj JA, Smith K, Rennie MJ. Myofibrillar and collagen protein synthesis in human skeletal muscle in young men after maximal shortening and lengthening contractions. Am J Physiol Endocrinol Metab 2005;288:E1153-9.
16. Hollander MS, Baker BA, Ensey J, Kashon ML, Cutlip RG. Effects of age and glutathione levels on oxidative stress in rats after chronic exposure to stretch-shortening contractions. Eur J Appl Physiol 2010;108: 589-97.
17. Baker BA, Hollander MS, Kashon ML, Cutlip RG. Effects of glutathione depletion and age on skeletal muscle performance and morphology following chronic stretch-shortening contraction exposure. Eur J Appl Physiol 2010;108:619-30.
18. Warner SE, Sanford DA, Becker BA, Bain SD, Srinivasan S, Gross TS. Botox induced muscle paralysis rapidly degrades bone. Bone 2006;38:257.
19. Rauch F, Hamdy R. Effect of a single botulinum toxin injection on bone development in growing rabbits. J Musculoskelet Neuronal Interact 2006;6:264-8.

20. Poliachik SL, Bain SD, Threet D, Huber P, Gross TS. Transient muscle paralysis disrupts bone homeostasis by rapid degradation of bone morphology. Bone 2009.
21. Rittweger J, Beller G, Armbrecht G, Mulder E, Buehring B, Gast U, Dimeo F, Schubert H, de Haan A, Stegeman DF, Schiessl H, Felsenberg D. Prevention of bone loss during 56 days of strict bed rest by side-alternating resistive vibration exercise. Bone 2009;PMID: 19732856.
22. Manske SL, Boyd SK, Zernicke RF. Muscle and bone follow similar temporal patterns of recovery from muscle-induced disuse due to botulinum toxin injection. Bone 2010;46:24-31.
23. Busse B, Hahn M, Soltau M, Zustin J, Puschel K, Duda GN, Amling M. Increased calcium content and inhomogeneity of mineralization render bone toughness in osteoporosis: mineralization, morphology and biomechanics of human single trabeculae. Bone 2009;45:1034-43.
24. Harlow HJ, Lohuis T, Beck TD, Iaizzo PA. Muscle strength in overwintering bears. Nature 2001;409:997.
25. Donahue SW, McGee ME, Harvey KB, Vaughan MR, Robbins CT. Hibernating bears as a model for preventing disuse osteoporosis. J Biomech 2006;39:1480-8.
26. McGee ME, Maki AJ, Johnson SE, Nelson OL, Robbins CT, Donahue SW. Decreased bone turnover with balanced resorption and formation prevent cortical bone loss during disuse (hibernation) in grizzly bears (Ursus arctos horribilis). Bone 2008;42:396-404.
27. McGee-Lawrence ME, Wojda SJ, Barlow LN, Drummer TD, Castillo AB, Kennedy O, Condon KW, Auger J, Black HL, Nelson OL, Robbins CT, Donahue SW. Grizzly bears (Ursus arctos horribilis) and black bears (Ursus americanus) prevent trabecular bone loss during disuse (hibernation). Bone 2009;45:1186-91.
28. Rittweger J, Simunic B, Bilancio G, Gaspare De Santo N, Cirillo M, Biolo G, Pisot R, Eiken O, Mekjavic IB, Narici M. Bone loss in the lower leg during 35 days of bed rest is predominantly from the cortical compartment. Bone 2009;44:612-8.
29. Utz JC, Nelson S, O'Toole BJ, van Breukelen F. Bone strength is maintained after 8 months of inactivity in hibernating golden-mantled ground squirrels, Spermophilus lateralis. J Exp Biol 2009;212:2746-52.
30. Noble BS, Stevens H, Loveridge N, Reeve J. Identification of apoptotic changes in osteocytes in normal and pathological human bone. Bone 1997;20:273-82.
31. Hedgecock NL, Hadi T, Chen AA, Curtiss SB, Martin RB, Hazelwood SJ. Quantitative regional associations between remodeling, modeling, and osteocyte apoptosis and density in rabbit tibial midshafts. Bone 2007;40:627-37.
32. Aguirre JI, Plotkin LI, Stewart SA, Weinstein RS, Parfitt AM, Manolagas SC, Bellido T. Osteocyte apoptosis is induced by weightlessness in mice and precedes osteoclast recruitment and bone loss. J Bone Miner Res 2006; 21:605-15.
33. Mann V, Huber C, Kogianni G, Collins F, Noble B. The antioxidant effect of estrogen and Selective Estrogen Receptor Modulators in the inhibition of osteocyte apoptosis *in vitro*. Bone 2007;40:674-84.
34. Emerton KB, Hu B, Woo AA, Sinofsky A, Hernandez C, Majeska RJ, Jepsen KJ, Schaffler MB. Osteocyte apoptosis and control of bone resorption following ovariectomy in mice. Bone 2010;46:577-83.