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Review Article

Hylonome

# What is new in neuro-musculoskeletal interactions?

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## Strain on bones, sheep and DXA machines (Frank Rauch)

### Growth Hormone (GH): Stronger muscles, stronger bones

It is well known that GH therapy of GH deficient children leads to a rapid increase in muscle mass. Hulthen et al. show that the reverse happens when GH therapy is stopped after final height is reached[1]. Lean body mass decreased by about 10% within two years after the discontinuation of GH treatment, whereas healthy age-matched controls (17 to 21 years old) kept increasing their lean body mass. Despite decreasing lean body mass in the GH deficient subjects, their muscle 'strength' remained stable. However, this compared unfavorably with the increasing muscle strength of healthy individuals.

You do not have to search far to find a solution to this problem. A paper by the same group of researchers in the same issue of JCEM[2] provides the expected answer: GH. They studied 21 patients with childhood-onset GH deficiency who now were 31 years old on average. GH therapy over five years was associated with an increase in lean body mass, muscle strength and bone mass.

GH is a great target for research, because it has a confusing number of effects that wait to be disentangled. A popular approach is to inject GH, measure a handful of things and conclude that GH actions are complex (meaning that it is hard to make sense of the data). Forwood et al. used a more successful strategy[3]. Two GH injections were given to rats at a 12 hour interval. One hour after the second injection, the rats' right tibiae were subjected to a single period of four-point bending and the bone response was measured by histomorphometry. GH had no effect on the non-loaded left tibiae and the mechanical stimulus on the right tibiae had no effect on controls that had not received GH. However, high-dose GH and high-load mechanical stimulation together led to a significant increase in bone formation. The authors concluded that GH modulates the responsiveness of bone tissue to mechanical stimuli by changing thresholds for bone formation. If this conclusion has a familiar ring to you, maybe it is because you remember a 1998 article from ISMNI's honorary president, where the same idea was put forward as a hypothesis[4].

Many of GH's actions are mediated by insulin-like growth factor-1. Overexpression of insulin-like growth factor-1 in the osteoblasts of mice had similar effects as injecting GH to rats: the response to mechanical stimulation was amplified[5]. Another analogy to the rat studies was that overexpression of insulin-like growth factor-1 alone or mechanical stimulation alone had little effect.

### DXA applications for ambitious users

Are you tired of predicting other people's future from the printout of your DXA machine? If so, there are some new ideas that might stir your interest.

Duan and colleagues show new ways to make use of lumbar spine densitometry[6,7]. They start out from the idea that the occurrence of non-traumatic vertebral fractures depends not only on bone strength but also on the forces that are applied to the vertebra. This may appear trivial to outsiders, but is nevertheless revolutionary in this particular research area. Traditional densitometry completely ignores the forces that challenge bone strength. Duan and colleagues estimate the strength of the L3 vertebral body from an antero-posterior and a lateral DXA scan. The forces that are applied to this vertebral body are assumed to depend on body weight, height and the lever arm of the erector spinae muscle. The length of this lever arm is measured on the lateral spine scan. Forces and bone strength are combined into a number dubbed 'Fracture Risk Index'. This Index thus not only has a biomechanical basis, but also can be determined with widely available technology and has a catchy name. Even better, the Fracture Risk Index comes with a brand-new 'fracture threshold', which happens to be 1. Thus, there are all the ingredients that should guarantee a successful career of this index within the osteoporosis research community.

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Duan and colleagues go on to show that in young adult men and women there is a similar relationship between bone strength and mechanical load. With aging, men are more successful than women in keeping bone strength adapted to loads, because they better compensate the decrease in bone density by an increase in cross-sectional bone size. This might explain the higher incidence of vertebral fractures in women. The importance of these findings is stressed by the fact that they are shown twice in the same issue of JBMR[6,7].

### Small strains, big gains – the story of eight sheep, told in three papers

Few sheep can claim to be famous. Dolly is a notable exception, and so are Dr. Rubin's eight shaking sheep[8-10]. The scientific career of this little flock started brilliantly with a Nature publication[8]. All they had to do for that was to stand on a small oscillating plate (30 Hz) for 20 minutes on working days. Only the hinds limbs were placed on this plate and were thus subjected to a vertical ground-based vibration that caused minimal strains (less than 10 μstrain) within the bones of the lower legs. When not busy with their experimental work, these sheep "joined the controls to roam freely in a pasture area", as the authors poetically point out. This peaceful way of life ended abruptly after one year, when all the sheep were killed. When analyzing the proximal femur, it was found that the mechanically stimulated sheep had a 34% higher trabecular bone density than controls. No difference between groups was detected in cortical bone and in the non-stimulated radius.

Readers who like to see more text around the numbers can find a detailed description of these data in a recent issue of Bone[9]. In still another publication we learn that the effects of mechanical stimulation were less impressive in the distal femur than in the proximal femur[10]. Trabecular density increased by only 10.6% at that site. Nevertheless, trabecular bone stiffness and strength in the proximal femur were 12 and 27% higher, respectively, in stimulated than in non-stimulated sheep. You do not have to be a prophet to foresee that these encouraging results will spark off a large number of studies and probably an even larger number of publications.

### Attention: Barefoot walking deforms your metatarsals!

Just in time for the summer season there is new information on the effects of barefoot walking[11]. Eight volunteers had staples inserted into the dorsal cortex of their second metatarsal and the strains were measured during slow walking (3 km/h). This mild exercise produced mean compressive strains of about 1500 μstrain, which is three times more than the effect of walking on the anterior tibia[12]. Interestingly, the strain in the second metatarsal increased even further when the subjects were mildly fatigued after a walking time of up to one hour. Thus, muscles do not only put loads on the bones, they also protect the bones. When the protector muscles tire out, loads increase and stress fractures can occur.

## Aging muscles, mitochondria, and paradigms (Jörn Rittweger)

### Sex steroids and muscle

In science, transpiration is quite as important as inspiration. This is particularly true in the field of exercise and muscle physiology, and it may also apply to the valuable data that Bhasin et al. furnish[13]. The authors investigated the dose-response relationship of testosterone effects in 61 healthy young men. Endogenous testosterone release was blocked in these men and weekly testosterone doses between 25 and 600 mg were given instead. It has long been known that testosterone has an effect on body composition, muscle mass and function, plasma lipid levels, haemoglobin etc. Yet, the dose response curves of these effects have never been studied in a systematic way. The authors now report a clear dose-dependance regarding testosterone effects on body composition, muscle size, force and power, haemoglobin and high-density lipoprotein concentrations. Mating behaviour, prostate specific antigen, bilirubin and other measures taken for safety reasons were not affected. Unfortunately, changes in bone were not assessed. Obviously, outside of the 'bone field', androgens are famous for effects other than their osteogenic potential.

As to testosterone's female counterpart, estrogens, their relationship to muscle is less clear. Conflicting results have been published concerning the effect of estrogens on muscle mass, function and metabolism. Now Lemoine et al.[14] turn things around and report effects of endurance exercise on oestrogen α receptor transcripts in rat skeletal muscle. The investigators had male and female rats run on a treadmill for 7 weeks. Thereafter, they harvested the gastrocnemius muscles and compared them to those of gender-matched control animals. Reverse transcriptase PCR revealed elevated oestrogen α receptor mRNA levels only in exercised females. As the authors point out, this finding may have implications for anabolic and metabolic effects in female skeletal muscle and may help explain the elevated frailty of elderly women.

### Muscle aging and the mitochondrion

Endurance, i.e. the capacity to maintain power over time, is one of the key characteristics that decline with age. In terms of (muscle) physiology, endurance is guaranteed by mitochondrial aerobic metabolism. Two recently published studies are focussing on aspects of the aging mitochondrion.

Kerner et al. observed that 24-month-old rats had a 20 to 25% lower skeletal muscle mitochondrial content than 6-month-old 'youngsters'[15]. The difference between age groups

may even have been underestimated. This is because the entire musculature of the hind limb was assessed, which in aged animals is expected to have a higher percentage of slow twitch fibers. These fibres are usually specialized on oxidative metabolism and therefore have a large number of mitochondria. The older animals also had a 68% lower amount of uncoupling protein 3 (thermogenin), which has previously been found to be elevated in immobilized muscles[16]. Physiologically, this should have two consequences: first, the degree of efficiency in oxidative metabolism should decrease. Second, the abundance of reactive oxygen species will increase (!) not as a cause, but rather as a consequence of aging effects.

If anti-aging strategies are to preserve muscle function, they have to inhibit mitochondrial decline. This is where the regulation of mitochondrial biogenesis comes into play. A recent paper by Wu et al. maintains that calmodulin-dependent protein kinase IV (CaMKIV) plays an important role in this respect[17]. The authors investigated two transgenic mouse models that expressed CaMKIV* (an artificial, constitutively active variant of CaMKIV) in skeletal muscles. These transgenic strains exhibited increased levels of genes encoding mitochondrial proteins. There also was an increased mitochondrion content in fast twitch muscles, an improved recovery after fatigue and an increased percentage of fast twitch fibers in these muscles. These findings may improve our understanding of pathways that adapt muscle cells to metabolic demands. These are probably different from the mechanisms that regulate myosin synthesis and thus mechanical power output capacity[18]. The authors regard peroxisome proliferator-activated receptor γ coactivator 1 (PGC-1) as a possible mediator. PGC-1 is known to influence, among other things, uncoupling proteins (see above). Indeed, PGC-1 was increased in CaMKIV* transgenic mice.

## Cross education

It is quite hard to get exercise effects without effort: no pain, no gain[19]. Yet, there are ways to cheat. For example, if you expose your right biceps brachii muscle to resistance exercise, its isometric force will increase, hopefully. However, your left untrained biceps may become stronger at the same time, even though it was not trained. This well-known but rarely discussed phenomenon is called cross education. It is probably caused by both peripheral (muscle hypertrophy[20]) and central effects. As to the latter, an improvement of intra-muscular co-ordination, recruitment patterns[21], and central nervous excitability have been suggested.

Shima at al. investigated cross education effects during training and detraining of the plantar flexors[22]. Training increased peak force during maximum voluntary contraction (MVC) by 18.6% on the trained limb and by 7.3 % on the contralateral limb. After 6 weeks of detraining, 11.0% and 2.9% of the MVC gain were preserved, respectively. Concomitant changes were observed in integrated EMG and in the degree of voluntary activation as assessed with the twitch interpolation technique[23]. Thus, central nervous effects seem to play the major role in cross education.

## Shift the paradigm

The JMNI reader may be aware of (and hopefully taking part in) the paradigm shift that is going on in the 'bone field'. In simplistic terms, that new paradigm is: structures adapt to their usage, and they do so by two different processes, i.e. modeling and remodeling. Other fields may have their own paradigm shifts. An illustration of this is given by Taub, Uswatte and Elbert, who review 'new treatments in neurorehabilitation founded on basic research'[24]. It has long been known that the central nervous system is not 'hard-wired' but exhibits plasticity[25]. In their article, the authors summarize recent evidence that central plasticity may be exploited for rehabilitation strategies. One such strategy is constraint-induced therapy. This is as peculiar as the 'cross education' mentioned above: artificial impairment of undisrupted functions (e.g., the less damaged arm) improves the disrupted functions (the more damaged arm). The authors suggest a model in which the 'learned non-use' is overcome by breaking the positive feed-back loop of frustrated function overwhelming activity of non-disrupted functions. These principles were first developed in the sensomotor context, and only recently have they been transferred to the treatment of aphasia, focal hand dystonia and dyslexia.

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