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Review Article

Hylonome

What is new in neuro-musculoskeletal interactions?

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Neuromuscular science: From ion channels to chocolate eating (Jörn Rittweger)

New news about Ca^{++} and phosphate

Muscle and bone tissues have quite a lot in common: modeling and remodeling, adaptation to mechanical usage, questions of ion exchange and crystallization... An illustration for this is provided in a publication that investigates the functional relevance of phosphate ions (P_i) in rabbit muscle[1]. During fatigue, the P_i released from ATP accumulates in the cytosol. At the same time, the Ca^{++} efflux from the sarcoplasmic reticulum (SR) in response to an action potential is inhibited. Laver et al. now present data showing that during fatigue, P_i diffuses through so-called chloride channels (their role in P_i exchange was unknown when they were scientifically baptized) into the SR. There, Pi precipitates with Ca^{++}, preventing further diffusion of both ions. Thus, calcium phosphate seems to play a role not only in the bones but also in the muscles.

A more traditional paper reports on the SR Ca^{++} release and storage in cast-immobilized humans[2]. As one would have expected, muscle size and power decline in that situation. But based on *in vitro* analyses of muscle biopsies during the immobilization, the authors report that the maximum Ca^{++} uptake decreases with immobilization, whereas Ca^{++} release and also the activity of the Ca^{++}-ATPase remain normal. Intracellular Ca^{++}-levels were not measured in this study. However, a long-term increase of intracellular Ca^{++} is considered as one of the mechanisms leading to muscle atrophy. On the other hand, muscle contractions are quantitatively triggered by rises in intracellular Ca^{++} levels. Possibly, the muscular adaptation to its usage is affected not only by how much, but also when the Ca^{++} escapes from the SR to the cytosol.

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Exercising muscles...

It may matter not only *what* you eat, but also *when* you eat, particularly if you are aged[3]. In 13 men of 74 ± 1 years of age, Esmarck et al. observed a hypertrophy of the quadriceps femoris muscle after resistance exercise only when an oral protein supplement was taken immediately after the exercise, but not when it was ingested two hours later. These effects are unlikely to be caused by energy metabolic effects, because the insulin and glucose responses were comparative in both groups. Other studies have shown that resistance exercise is effective in the elderly even without specific nutritional measures. It is therefore somewhat surprising that in this study the control group did not have any muscle hypertrophy despite exercise. However, considering nutrition in training programs may be worthwhile in the elderly.

Wretman et al. addressed the question of how exercise affects muscles on the cellular level[4]. They investigated the responses of MAP (mitogen activated protein) kinase phosphorylation (= activation) to concentric and eccentric contraction and to passive stretch in isolated rat muscles. Different kinds of MAPs are known as intracellular signals of cell differentiation and adaptation. Concentric contractions and mild stretch eliciting metabolic stress increased only one of the MAPs investigated ($MAP^{erk1/2}$). These results may be helpful to understand how Mother Nature has implemented muscle hypertrophy and its adaptation to metabolic demands.

... and measuring them

In the August copy of the Acta Physiologica Scandivaca you will find a great deal of relevant information, presented in quite a practical way[5,6]. In a very clear and careful study, Fukunaga et al. report that the physiological cross-sectional area (PCSA) predicted about 90% of the maximum voluntary torque in 26 university students. The PCSA was assessed from the muscle volume, pennation angle and fiber length, the latter two being measured by ultrasound imaging. PCSA is usually assessed by magnetic resonance imaging, but here the authors show that ultrasound imaging is almost quite as good – but much cheaper.

In the same issue, Maganaris demonstrates that the

length-force relationship for single muscle fibers is actually physiologically relevant[6]. Every medical student becomes acquainted with this curve at least once. You remember, this curve tells you that a sarcomere develops its peak isometric tension at a length of 2.2 nm. It has often been questioned if this curve has any practical implications, but the author now shows that this is the case. Measuring isometric force, and assessing the lever-arms by MRI and the muscle pennation angle by ultrasound imaging at different joint angulations, it turns out that in humans the soleus and tibialis anterior muscles usually work in the raising part of the force-length curve: the longer the muscle, the greater its isometric force.

Some goodies for the brain

One of the symptoms of Parkinson's disease is the reduction in stride length with unchanged step frequency. In the past years, electrical stimulation of the subthalamic nucleus (STN) has been investigated as a new therapeutic strategy. In an interesting paper from Lücking's group[7], the effects of STN stimulation on gait are compared with the pharmacological therapy with L-DOPA. Both strategies seem to be about equally effective and able to reinforce each other. By either of the two methods, stride length increases to about normal, with the frequency unchanged, and the gait becomes generally more "swinging". It will be interesting to follow-up these patients and see whether the positive effects of STN stimulation wear off in the same way as it is often observed with L-DOPA.

One of the most exciting present fields of brain research is the neurogenesis in adult mammals. This process was first detected in the hippocampus, but later was also reported in the subventricular zone in the lateral walls of the 1st and 2nd ventricles. Most likely, the newly "born" neurons are involved in learning and in the consolidation of memory[8]. It now seems that astrocytes give rise to these new neurons[9]. This is surprising, inasmuch as the astrocytes are part of the macroglia, which in the ontogenesis separate relatively early from other neuronal progenitors. It may turn out that the new finding is a major step forward in the identification of a physiological process which in the long run can be exploited for therapeutical strategies of brain repair – at least that is the hope.

Finally, some food for thought with particular relevance to the Christmas season. As is widely experienced during that time, chocolate may evoke either pleasant or unpleasant feelings, depending on the amount one has ingested. Small et al.[10] studied this phenomenon in a very elegant study. Using positron emission tomography they measured regional cerebral blood flow in response to the 1st to 7th bar of chocolate eaten by the test subject. The authors found that some brain regions (such as the posterior cingulated cortex) were activated both during pleasant and aversive chocolate feeding, whereas others were exclusively activated in response to pleasant chocolate intake (insula and orbitofrontal cortex). These findings suggest that different cortical systems regulate food intake, one responsible for "reward", and the other for "punishment". This study could promote our understanding of eating disorders and, more practically, could help JMNI readers explain their feelings after end-of-the year overfeeding.

Skeletal science: From triple jumps to culture dishes (Frank Rauch)

Jumping rats and people

A new jumping rats study has emerged from a laboratory that is known for its fit animal population[11,12]. This time their rats did 10 jumps per working day to a height of 40 cm. After 8 weeks of this training, dry weight, ash weight and outer size of tibial shafts had increased compared to those of sedentary rats. The ultimate breaking force in jumpers was increased by more than a third, irrespective of whether they were ovariectomized prior to training or not.

Heinonen et al. used non-invasive techniques to examine eight of Finland's best triple jumpers[13]. These individuals had a 24% higher cross-sectional cortical area in the tibial midshaft than well-matched non-triple-jumping controls, who were quite active in other sports. At the distal tibia, the cortical thickness and trabecular density of triple jumpers was higher by 56% and 18%, respectively.

These results are in accordance with mechanostat theory which states that loads above a certain threshold should turn on the bone modeling process and thereby increase bone strength. Maximal ground reaction forces were about 5 times body weight in the rats and about 20 times body weight in triple jumpers. Loads on the tibiae were not evaluated in these studies. However, as the muscles creating these ground reaction forces use unfavorable lever arms, the actual load on the tibia can be expected to be higher than ground reaction force in most phases of a jump cycle.

How to study musculo-skeletal interactions?

More and more bone-oriented investigators are discovering muscle. With this discovery comes the problem of how to study muscle-bone relationships? Most bone laboratories do not have specialized equipment for examining muscles and it may be difficult to obtain a functional muscle measure in small animals. Li et al. demonstrate that grip strength, one of the most popular muscle parameters in human studies, can also be determined in mice[14]. Let the mouse grasp a bar that is connected to a force transducer and then slowly pull the mouse up by the tail. The mouse will cling to the bar as long as it can and the maximal force reading is noted as the mouse's grip strength. Although grip strength is known to have a high variability and to depend on mood and motivation of the study participant, the authors found a significant relationship between grip force and humerus breaking force. This association persisted even after statistically "controlling" for areal bone mineral density. It was therefore concluded that the analysis of muscle force should complement densitometry as a tool for fracture forecast.

Clinical muscle-bone researchers have to confront the question what they actually want to study. What is the property of muscle that is influencing bone? And what is the relevant bone property susceptible to be influenced by muscle? Recent studies in healthy adults demonstrate that there is a puzzling number of combinatorial possibilities when clinical muscle and bone measures are combined[15-17]. For example, you can compare isokinetic quadriceps strength to areal BMD of the femoral neck[16], grip strength to radius strength-strain index[15] or regional lean body mass to areal BMD[17]. And then you need a motivated biostatistician to tell you whether "muscle predicts bone", even after adjustment for multiple confounders. It does, according to these studies. The clinician might look at all those multiple regression analyses with due respect - and hope all this can eventually be translated into concepts that are simple enough to be of practical use.

Regarding practical utility, Ringsberg et al. are already a step ahead[18]. They studied a large cohort of elderly women who had participated in physical activity programs over the past 20 years and compared them to non-exercising women of the same age. The trained women had higher quadriceps and grip strength, had better postural stability and walked faster. They also had had fewer "fragility fractures", although areal BMD at the radius was the same in the two groups. It appears from this study that exercising can reduce fracture rates and that areal BMD at the radius was not a particularly useful fracture prediction index in these women. Unfortunately, this type of retrospective study can not tell us whether the exercising women had had fewer fractures because they were exercising, or whether they were able to exercise because they had had fewer fractures.

What about neuro-skeletal and skeleto-neural interactions?

While muscle-bone studies are becoming more popular, relatively little is known on the direct nerve-muscle connection. Yet there is some clinical evidence for such a connection, as patients with cerebral trauma can have increased callus formation in fractured limbs. Li et al. studied the reinnervation of tibia fracture sites in rats[19]. There was rapid and abundant sprouting of nerve fibers in the fracture region as early as three days after fracture and even before vascularization of the callus started. No functional studies were done, but it was concluded that since the nerves are there, they should do something.

Skeletal cells may also have a direct influence on nerve cells. Asmus et al. showed that primary periosteal cells and osteoblast cell lines release a factor that induces choline acetyltransferase in sympathetic neurons[20]. In this way, the periosteum could alter the transmitter properties of its sympathetic innervation. Another bone-nerve interaction was described by Togari et al.[21]. These authors found that both human osteoblastic and osteoclastic cells express diffusible axon guidance molecules, at least in the cell culture dish. Thus, the neuro-skeletal interaction field seems to be quite typical for the state of present skeletal biology: We have only a dim idea of what these nerves are doing in bone, but at least we know molecular mechanisms that "regulate" them.

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