

# CMRC Annual Report, 2004

## Results obtained

### ***Research area 1. Regulation of carbohydrate and fat metabolism. Relationship with insulin sensitivity/-resistance and type 2 diabetes.***

FAT/CD36 is a fatbinding protein, and we have shown that this protein is located in the surface membrane of muscle cells. However, a much higher content is found in the endothelium cells lining the muscle capillaries. We have also shown that type 1 muscle fibres, which have a high fat oxidative capacity, contain more FAT/CD36 than type 2 fibres. Furthermore, FAT/CD 36 co-localizes with caveolin 3, a muscle specific structural protein in the caveolae of the sarcolemma. Finally, we have found that females compared with men have more FAT/CD 36 and caveolin 3 and also more caveolin 1, which is structural protein in caveolae of endothelium and fat cells.

We have found that transport of fatty acids into muscle cells is in part mediated by proteins. However, the transmembrane transport of fatty acids is not limiting fat metabolism in muscle. Our studies indicate that the regulation is exerted at the fatty acid transport into the mitochondria. This transport requires that the fatty acids are coupled to carnitine, which may also bind to acetate derived from carbohydrate metabolism. We find that the concentration of free carnitine plays a major role for the fine tuning of fat oxidation during exercise. Our studies also indicate that an increase in the activity of the enzyme 5'AMP-dependent protein kinase (AMPK) in muscle probably is important for the increase in fat oxidation that occurs with exercise.

Fatty acids may be released from the triglyceride depots in muscle cells. However, it is controversial whether intramyocellular triglyceride is an important energy source during exercise in man. We have studied this issue by microdialysis. We found that muscle cells release glycerol at rest and at low work intensities, but not at high intensities. This may indicate that triglyceride breakdown in muscle is maximal at low exercise intensities. We have also studied the regulation of the enzyme Hormone-sensitive lipase (HSL), which regulates the breakdown of the triglyceride stores in muscle. We measured the phosphorylation of 2 of the 5 known phosphorylation sites of HSL. One of these sites (Ser 565) is phosphorylated by AMPK during exercise, but this does not increase the chemical activity of the enzyme.

We have worked on the regulation of the pyruvate dehydrogenase (PDH)-complex, which plays a key role in the choice of substrates for metabolism in muscle, and with PGC-1 $\alpha$ , which seems to be an important transcriptionactivating factor in cellular adaptations. We have studied the role of fatty acids on the regulation of PDH-kinase isoforms and PHD-phosphatase as well as on PGC-1 $\alpha$ . A fatty acid emulsion (Intralipid) was infused i.v. at rest and during exercise. The effect was evaluated on transcription and mRNA level and by measurement of PDH activity. The study showed that while PDHK4-expression was markedly upregulated both during rest and prolonged exercise, mRNA for the isoforms PDHK1 and PDHK2 was unchanged. Furthermore, PDH phosphatase 1 mRNA was downregulated during prolonged exercise. Recombinant PDHK4 and PGC-1 $\alpha$  protein have been cloned and expressed in E.coli in order to allow us to produce antibodies against these peptides.

We have studied possible intracellular signaling mechanisms involved in contraction-induced gene activation. We have used cell cultures to study the calcium-mediated regulation of the PDHK4 and PGC-1 $\alpha$  genes, and we have used mice that do not express AMPK to study the role of this enzyme in the regulation of several genes known to respond to exercise. The cell culture study showed that the calcium-ionophore ionomycin markedly upregulates PGC-1 $\alpha$  mRNA but not PDHK4 mRNA. Moreover, the studies showed that inhibition of calcineurin abolishes the ionomycin-elicited upregulation of PGC-1 $\alpha$ , whereas inhibition of CAMK II and IV only decreases the effect of ionomycin to a small extent. Regarding the role of AMPK we found that the increase in transcription and mRNA levels of several genes seen after an exercise bout, e.g. PGC-1 $\alpha$ , HKII, FOXO1 and PDK4, is normal in mice that do not express  $\alpha$ 1 or  $\alpha$ 2AMPK. It follows that AMPK activity is not necessary for these responses.

Adding to the above studies of acute exercise, we have shown that chronic pharmacological activation of AMPK increases the expression of several proteins in muscle (e.g. HKII, GLUT4, Cyt.C and GS). This response is completely abolished in the absence of  $\alpha 2$ AMPK. In contrast, the response to training is intact. However, in resting muscle many mitochondrial markers are downregulated, when  $\alpha 2$ AMPK is missing. This may explain why the capacity for resynthesis of ATP is reduced in mice missing  $\alpha 2$ AMPK. For instance, during running muscle ATP levels decrease while IMP concentrations increase markedly in these animals.

In other studies of mice, which do not express either the  $\alpha 1$  or the  $\alpha 2$  subunit of AMPK we have shown that  $\alpha 2$ AMPK, but not  $\alpha 1$ AMPK, regulates glucose transport, when AMPK is pharmacologically stimulated. However, the increase in  $\alpha 2$ AMPK seen during exercise is not necessary for the accompanying increase in glucose transport. Using similar protocols we have now proved that glycogen synthase (GS) is an AMPK target in intact muscle. By application of phosphospecific antibodies we have shown that serin 7 in GS is phosphorylated by AMPK and that this decreases GS activity. In line with the regulation of glucose transport, apparently it is  $\alpha 2$ AMPK, but not  $\alpha 1$ AMPK, that is involved in GS regulation. During exercise serin 7 of GS is phosphorylated. However, this phosphorylation is intact in the absence of  $\alpha 1$  and  $\alpha 2$ AMPK indicating that other GS-kinases are responsible for this phosphorylation during exercise. The overall conclusion is that in resting muscle AMPK is necessary for increases in oxidative glucose metabolism and maintenance of energy balance. In line with this, we have found that basal AMPK activity as well as the increases in AMPK activity in muscle elicited pharmacologically or by exercise are diminished in animals or humans on a carbohydrate enriched diet. Whether the increased supply of glucose and/or the resulting accumulation of glycogen is involved in this regulation is not known yet.

Previous studies have indicated that AMPK plays a role in the exercise-induced increase in insulin sensitivity in muscle. Therefore, we have measured the expression and activity of the isoforms of all known AMPK-subunits in muscle from healthy subjects. We found that they vary in response to both endurance and strength training. In particular, we found a marked downregulation of the regulatory  $\gamma 3$  subunit with training, while the  $\gamma 1$  subunit was upregulated. The functional significance is not known yet, but some studies indicate that  $\gamma 3$  is involved in glucose/glycogen metabolism in resting muscle. A substitution of  $\gamma 3$  with  $\gamma 1$  also means that the average AMPK complex will be more sensitive to AMP. It is not known how this is an advantage for the trained muscle. However, trained muscle has a higher basal AMPK activity and ACC-phosphorylation, a fact which may explain the higher fat oxidation in trained compared with untrained muscle.

AMPK has been proposed both to be involved in development of type 2 diabetes (T2DM) and to be a possible target for treatment of diseases with insulin resistance. However, our studies indicate that in muscle of T2DM patients the expression of the various isoforms of the subunits of AMPK as well as AMPK activity are intact. So, defects in the AMPK system do not play a role in T2DM.

We have for years been interested in explaining the defects in muscle of T2DM patients resulting in the reduced non-oxidative glucose metabolism characterizing these patients. Because GS is rate limiting for the conversion of glucose to glycogen we have chosen to study the regulation of this enzyme with the aim of finding defects in the signal from the insulin receptor. We have raised a series of antibodies against GS phosphorylated at each of the 9 known phosphorylation sites. We are presently studying the specificity of these antibodies and developing methods to exactly quantitate the phosphorylation at specific sites. This is essential in the evaluation of e.g. dephosphorylations. So far we have shown that GS is hyperphosphorylated at serin 2+2a, but it is not known whether this explains that insulin-induced activation of GS is impaired in T2DM patients.

We have shown that in first degree relatives of T2DM patients training increase insulin sensitivity, while insulin secretory capacity does not change.

The function of the t-tubules in skeletal muscle has been thought to be spreading of the membrane depolarization stimulus from the surface to the interior of muscle cells thereby mediating the excitation-contraction coupling. We have now provided evidence that they also serve to transport energy substrates and hormones to the interior of muscle cells. By confocal microscopy we have been able in anesthetized mice to follow in real time the diffusion of fluorescent insulin into the t-tubules. This was accompanied by a progressing activation of insulin receptors in the t-tubules and local translocation of glucose transporting protein (GLUT4) to these tubules.

We have previously shown that training increases the content of GLUT4 in muscle of healthy subjects and T2DM patients. We have now used confocal microscopy to study whether this increase is equally distributed on the various intracellular GLUT4 containing structures. This was not so. With training more small GLUT4 vesicles are formed, which can be recruited by insulin. So, the GLUT4 vesicles existing prior to training are not able to store more GLUT4, and consequently new vesicles have to be formed, when extra GLUT4 is synthesized.

In man we have found that after prolonged exercise the concentration in muscle of ceramide (a lipid) is increased. On the other hand, the ceramide concentration is influenced neither by insulin or diabetes. After a high-fat meal the concentration of triglyceride in plasma increases more in T2DM patients than in healthy subjects, a fact probably contributing to the increased tendency to atherosclerosis in the former. We have now shown that particularly in T2DM patients exercise taken after such a meal reduces the postprandial increase in plasma triglyceride.

Atypical protein kinase C (aPKC) may play a key role in metabolic regulation. We have studied the influence of exercise intensity on the activity of aPKC in man. To our surprise a marked increase in aPKC activity was found already at a low work load (35% of maximal oxygen uptake) and no further increase occurred at higher loads.

In addition to muscle metabolism we have also studied brain metabolism during muscular exercise. We have shown that the brain takes up and metabolizes considerable amounts of lactate, when lactate is available. Together with glucose uptake this means a considerable carbohydrate uptake independent of hormone action, when brain activity is high during intense exercise. The uptake of carbohydrate varies with brain activity being highest at intense exercise including both arms and legs.

## ***Research area 2. Ion transport in muscle and its importance for metabolism, blood flow and fatigue.***

In a series of studies we have explored the progressive increase in muscle oxygen uptake with duration of exercise at a constant intensity (the so called "slow component"). By various manipulations and analysis of high number of single muscle fibres we have shown that the recruitment of muscle fibres play a major role for the "slow component". By analysis of single fibres and muscle temperature measurements we have also found that single biopsies taken from the vastus lateralis muscle before and after knee extensor exercise are representative of the whole muscle. This finding is reassuring in regard to interpretation of both previous and future studies. Finally, we have found that after a period of training, compared with findings before training, the oxygen uptake in muscle in the beginning of exercise is higher, if the work is intense, but not if it is mild. This may also reflect that muscle fibre recruitment is important for muscle oxygen uptake at the beginning of exercise.

We are examining which factors control the amount of important proteins, e.g. Na<sup>+</sup>-K<sup>+</sup> pumps and lactate transporters in skeletal muscle of man. It has become clear that just one bout of exercise increases mRNA levels of the subunits of the Na<sup>+</sup>-K<sup>+</sup> pump, and that the control is primarily local. Training causes a marked increase in Na<sup>+</sup>-K<sup>+</sup> pump subunits in muscle of both healthy subjects and T2DM patients. This probably explains that interstitial concentrations of potassium in muscle both during light and severe exercise are lower than before training. The changes correlate with improved performance capacity after training, a finding supporting the view that potassium plays an important role in development of fatigue during exercise. Also other ion transport systems in muscle adapt to training. An example is an increase in content of the lactate-proton cotransporter, which explains the diminished decrease in intramyocellular pH during exercise after training. The negative effect of a low pH is ameliorated and we have shown that another result is a diminished release of potassium, both changes improving work performance.

## ***Research area 3. Hormone secretion from fat and muscle cells during exercise.***

We have previously shown that working muscles produce the cytokine IL-6. Now, we have extended this observation by showing: That IL-6 is involved in regulation of AMPK activity and glucose homeostasis during exercise; that antioxidants diminish IL-6 production in muscle; that IL-6 induces lipolysis and lipid oxidation in

vitro and in vivo; that during exercise IL-6 mediates antiinflammation (TNF $\alpha$  suppression) in humans, a finding confirmed in IL-6 knock out mice; that IL-6 plays a role in regulation of the ironregulating hormone hepcidin; and that IL-6 expression in adipose tissue is regulated by insulin and epinephrine. Furthermore, we have established methods for studies of genetic polymorphism in cytokines and we have demonstrated a relationship between IL-6 and TNF $\alpha$  polymorphism and the metabolic syndrome. With stable isotopes we have shown that IL-6 increases insulin sensitivity, whereas TNF $\alpha$  induces insulin resistance.

We have shown that working muscle produces the cytokine IL-18. Furthermore, we have found high IL-18 mRNA expression in resting muscle in untrained subjects with inflammatory diseases. Our studies indicate that IL-18 is involved in apoptosis in adipose tissue (and secondary ectopic accumulation of lipid, e.g. in muscle) and, in turn, insulin resistance. In other studies we have shown that IL-18 is also expressed in human adipose tissue. IL-18 is associated with lipodystrophy in humans and in multivariate analyses strongly correlated with insulin resistance.

#### ***Research area 4. Central and peripheral circulation.***

It has not been clear why the arterial blood pressure has the height it has: Brain perfusion might be due to a "siphon action" eliminating gravity. However, in a study in which pressures were measured in both the veins draining the brain and in the cerebrospinal fluid, we have shown that no siphon action contributes to brain perfusion. The perfusion pressure of the brain depends on a complex interaction between the arterial and venous blood pressures. Thus, the venous pressure has only a protracted effect on brain perfusion in the upright position, because veins above the level of the heart are collapsed. These relationships have been described in a mathematical mode.

From the above it is clear that the importance of the arterial baroreceptors for blood pressure regulation has gained interest. We have shown that the fact that the arterial blood pressure is lower during exercise with both arms and legs than during exercise only with the arms reflects that the threshold of the arterial baroreceptors is set to regulate the actual blood pressure. In contrast, during vasovagal shock the circulation is not controlled from the baroreceptors, and simultaneous decreases in arterial blood pressure and heart rate is seen. In studies on elite skiers working maximally with the arms and/or the legs we have shown that during combined arm and leg exercise the arterial pressure pressure can only be maintained because the metabolic vasodilatation is counteracted, probably by sympathetic nervous vasoconstriction.

We have studied the effect of training on angiogenesis and blood flow in skeletal muscle. We used various approaches, e.g. sampling of interstitial fluid and application of this on cultured skeletal muscle and endothelium cells. Our data show that contraction increases the content of Vascular Endothelial Growth Factor (VEGF) mRNA in human skeletal muscle, primarily the isoform VEGF 165. Intensive training transiently increases the levels of VEGF mRNA in human muscle, the levels decreasing to pretraining levels after 6 weeks. The number of proliferating endothelium cells as well as the stimulating effect of muscle interstitial fluid on endothelium cell proliferation follow the same time course during training. Our results demonstrate that skeletal muscle cells are important in the regulation of angiogenesis, the effect in part being due to their release of VEGF and other vascular growth factors and because they release signaling substances stimulating the content of VEGF in endothelium cells. We have further extended these findings by showing that thromboxane and prostaglandin E2 are important for the regulation of VEGF in muscle and endothelium cells and for the effect of muscle on endothelium cell proliferation.

#### ***Research area 5. Studies of patients with monogenetic skeletal muscle diseases.***

In the molecular biology area we have expanded our original finding that mitochondrial DNA (mtDNA) can be inherited from the father, and not as previously thought only from the mother. We have now shown that paternal heritage occurs very rarely. We have also used the coexistence of paternal and maternal mtDNA to show that mtDNA can recombine.

Using stable isotopes we have shown that even patients with only one mutation in the gene for carnitine palmitoyl transferase II (CPT II) may have a deficient betaoxidation of fatty acids. This contrasts with the view

based on clinically overt cases that the condition is recessively inherited. Our finding may reflect that the CPT II molecule is a tetramer and so may be subject to a dominant negative effect of single mutations.

In the metabolic area we have shown that patients with the betaoxidation defect VLCAD have a normal basal lipid oxidation, whereas their lipid oxidation cannot increase with exercise. Interestingly, in these patients also mobilization of free fatty acids does not increase in response to exercise, a fact pointing to the existence of some hitherto not characterized feedback mechanism. We have done similar findings in CPT II patients. In patients with a partial or complete block of glycolysis we have found that they exhibit no "second wind" phenomenon during exercise. This agrees with the fact that this phenomenon is normally associated with administration of glucose.

### ***Research area 6. Interaction between muscle and adipose tissue. Relationship with everyday activities.***

We have studied the regulation of collagen synthesis in both intramuscular connective tissue and tendon in several investigations. With stable isotopes we have shown that a single bout of exercise increases collagen synthesis in connective tissue within 6 hours. This coincides with the exercise induced increase in myofibrillar protein. Thus, protein synthesis of connective tissue and contractile apparatus, respectively, are well coordinated in muscle. After repeated exercise we find an upregulation of growth factors (IGF-1 and its binding proteins as well as TGF-beta) in intramuscular connective tissue and tendon, and this occurs before an upregulation of collagen type 1 mRNA. The workinduced collagen synthesis is more prolonged in tendon than in muscle and this indicates, together with findings in bone and ligaments, that collagen synthesis is tissue specific and varies in magnitude between tissues in response to mechanical loading.

Human tendon has a high compliance and accordingly is well suited to absorb elastic energy, whereas aponeuroses and fasciae transduce force. Using isolated human tendons, both intact tendons and isolated fibrils, we have shown that even within a given tendon regional differences exist regarding compliance and strength. This is of central importance for the understanding of the regional appearance of overloading injuries in tendons. In the patella tendon we have found a close association between the areas with the weakest fibrils and the occurrence of injuries diagnosed clinically or by ultrasound examination.

We have shown that strength training induces muscle hypertrophy in various patient groups, e.g. patients with chronic obstructive lung diseases (COLD). Similarly, we have shown that the muscle atrophy accompanying hip replacement in patients with arthrosis can be prevented by training. The training causes an increase in strength, particularly in the rate of force development, which is closely related to the ability to carry out ordinary activities (e.g. rise from a chair, climb stairs) and which diminishes the risk of falling and of fracture.

We have found that heavy voluntary exercise has a profound effect on the intramuscular connective tissue, whereas nearly no damage is seen in myofibrils or cytoskeleton. We have also shown that a single bout of exercise can increase the activity and proliferation of satellite cells in human muscle. Apparently, satellite cells are not only involved in muscle regeneration upon extensive damage of sarcolemma but also play a physiological role in muscle adaptation to training.

Prostaglandins (PG) plays a central role for blood flow in tendon during exercise and together with NO also a role for blood flow in skeletal muscle. We have developed a procedure for graded blockade of these substances involving placement of several microdialysis catheters in a given muscle or tendon and local infusion of blocking drugs. With this methodology we have shown that increasing blockade of PG and NO is accompanied by decreasing blood flow in skeletal muscle and tendon.

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## Publications

### **Research area 1.**

#### **PhD-theses**

Morten Donsmark: Regulation and role of hormone-sensitive lipase in rat skeletal muscle. University of Copenhagen 2004.

Carsten Roepstorff: Regulation of lipid utilization in human skeletal muscle during exercise. University of Copenhagen, November 2004.

Kristian Vissing: Transcriptional regulation of skeletal muscle phenotype". University of Aarhus.

#### **Papers in accordance with the CMRC research strategy**

Bruce CR, Lee JS, Kiens B and Hawley JA. Postexercise muscle triacylglycerol and glycogen metabolism in obese insulin-resistant Zucker rats. *Obes Res* 12: 1158-1165, 2004.

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Donsmark M, Langfort J, Holm C, Ploug T and Galbo H. Contractions induce phosphorylation of the AMPK site ser(565) in hormone-sensitive lipase in muscle. *Biochem Biophys Res Commun*. 316: 867-871, 2004.

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Hojlund K, Mustard KJ, Staehr P, Hardie DG, Beck-Nielsen H, Richter EA and Wojtaszewski JF. AMPK activity and isoform protein expression are similar in muscle of obese subjects with and without type 2 diabetes. *Am J Physiol Endocrinol Metab* 286: E239-E244, 2004.

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#### **Papers giving an expression of other activities in which CMRC researchers are involved**

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Iqbal, S, L.S. Mørch, M. Rosenzweig and F. Dela. The outcome of bone mineral density measurements on patients referred from general practice. *J Clin Densitometry.* Accepted, 2004.

## ***Research area 2.***

### **PhD-theses**

Peter Krstrup: Muscle Oxygen Uptake and Energy Turnover During Dynamic Exercise in Humans. University of Copenhagen, August 2004.

Lotte Jensen: Regulation of VEGF, bFGF and capillary growth in skeletal muscle. University of Copenhagen, November 2004.

### **Papers in accordance with the CMRC research strategy**

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Krstrup P, Hellsten Y and Bangsbo J. Intense interval training enhances human skeletal muscle oxygen uptake in the initial phase of dynamic exercise at high but not at low intensities. *J Physiol* 559: 335-345, 2004.

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#### **Papers giving an expression of other activities in which CMRC researchers are involved**

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### **Research area 3.**

#### **Doctor of medical sciences theses (DMSc)**

Mogens Kappel: Immunological and hormonal responses to hyperthermia. With special reference to the role of stress hormones in mediating hyperthermia-induced immunomodulation. University of Copenhagen.

#### **Papers giving an expression of other activities in which CMRC researchers are involved**

Bruunsgaard, H., E. Bjerregaard, M. Schroll, B. K. Pedersen. Muscle Strength after resistance training is inversely correlated with baseline levels of soluble tumor necrosis factor receptors in the oldest old. *Am Geriatr Soc* 2004; 52(2): 237-41.

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#### **Papers giving an expression of other activities in which CMRC researchers are involved**

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## **Research area 4.**

### **Doctor of medical sciences theses (DMSc)**

Lars Nybo: Cerebral perturbations provoked by prolonged exercise. Københavns Universitet.

Frank Pott: Dynamic aspects of blood flow regulation. Københavns Universitet.

### **PhD-theses**

Henrik Lajer: Clinical and experimental aspects of cisplatin-induced hypomagnesemia. University of Copenhagen.

### **Papers in accordance with the CMRC research strategy**

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**Papers giving an expression of other activities in which CMRC researchers are involved**

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***Research area 5.***

**Papers in accordance with the CMRC research strategy**

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**Papers giving an expression of other activities in which CMRC researchers are involved**

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## **Research area 6.**

### **PhD-theses**

Charlotte Suetta: Muscle function in the elderly after hip-replacement surgery – effects of long term disuse and physical training. University of Copenhagen, June 2004.

Lars Rosendahl: Interstitial changes in trapezius muscle during repetitive low-force work. University of Copenhagen, November 2004.

### **Papers in accordance with the CMRC research strategy**

Andersen L, G Tufekovic, M Zebis, R Crameri, G Verlaan, M Kjær, C Suetta, P Magnusson, and P Aagaard. The effect of resistance training combined with ingestion of protein drink on muscle fibre size and muscle strength. *Metabolism*, in press, 2004.

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#### **Papers giving an expression of other activities in which CMRC researchers are involved**

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Rasmusen HH, and M Kjær. Fysisk træning, en effektiv behandling af katabolismen i skeletmuskulatur. Ugeskr.f.Læger, 166: 3490-3492, 2004.

Schiellerup P, Dyhr T, Rolain JM, Christensen M, Damsgaard R, Ethelberg S, Fisker N, Frost Andersen N, Raoult D, Krogfelt KA. Low seroprevalence of bartonella species in Danish elite orienteers. Scand J Infect Dis. 2004;36(8):604-6.

## Invited lectures

### **Research area 1.**

Flemming Dela:

9<sup>th</sup> Annual Congress of The European College of Sports Science. Clermont-Ferrand, France, July 2004.

Dansk Reumatologisk Selskab. Invited speaker: "Prevention and treatment of metabolic diseases: exercise related mechanisms. Kolding, Denmark, Sept. 2004.

Henrik Galbo:

"Intracellular signaling in contracting skeletal muscle", The 11th International D.E.S.A. (Diabetes, Exercise og Sports Association) Meeting, Montecatini Terme, Italy, 27.03. 2004.

Hans P.M. Mortensen Lauritzen:

"GLUT4 dynamics in skeletal muscle", Århus Universitetshospital, Institute of Experimental Clinical Research, May 2004.

Henriette Pilegaard:

IOC Pre-Olympic Congress, Thessaloniki, Greece, August 2004.

Erik A. Richter:

"AMPK 2204", Lorne, Australia, March 2004.

"State of the Art Lecture", American Diabetes Association, Orlando, USA, June 2004.

Peter Schjerling:

"Amplification efficiency in real-time PCR", QRT-PCR symposium, Symbion, June 2004.

B. Stallknecht:

"Træning og fedme", årsmøde i Dansk Idrætsmedicinsk Selskab og Fagforum for Idrætsfysioterapi, Copenhagen 2004.

Jørgen Wojtaszewski:

"AMPK 2004", Lorne, Australia, March 2004.

"Exercise, AMPK and insulin action", Baltic Summer School, Lund 2004.

### **Research area 2.**

Carsten Juel:

"Sarcollemmal transport of lactate, effect on muscle pH during exercise". European College of Sport Science meeting, France 2004.

### **Research area 3.**

Helle Bruunsgaard:

September 2004, Bethesda, USA, NIH. NIA Workshop on Inflammation, Inflammatory Mediators and Aging. Exercise and Cytokines in the elderly.

Bente Klarlund Pedersen:

March 2004, Stockholm, Sweden 7th Scandinavian Conference on Medicine and Science in Sports: Exercise and The Immune System.

May 2004, Stockholm Nobel Forum. International Symposium on Insulin Resistance and Diabetes. Cytokines and Insulin resistance.

May 2004, Prague, Czech Republic, 13<sup>th</sup> European Congress on Obesity. The role of IL-6 production by muscle.

June 2004, Copenhagen, Denmark, 5<sup>th</sup> International Conference on Walking in the 21<sup>st</sup> Century. Exercise and health.

June 2004, Vienna, Austria, The International Life Sciences Institute - ILSI Europe. Non-nutritional factors affecting immunity: Non-environmental factors modulating the immune system with special focus on exercise.

July 2004, Clermont-Ferrand, France, 9<sup>th</sup> Annual Congress of the European College of Sport Science: Exercise and overtraining – role of cytokines.

July 2004 Heidelberg, Germany, The Future of Health Care – New image of humans. Exercise and Cytokines (key-note speaker).

September 2004, Malmö, Sweden. Baltic Summer School. Exercise, cytokines and insulin resistance.

October 2004 Austin, Texas The American Physiological Society APS Intersociety Meeting.

The Integrative Biology of Exercise. Member of the scientific committee. Exercise and IL-6 – biological roles.

October 2004 Galveston, Texas. Visiting professor. Muscle-derived IL-6 and its role in insulin resistance.

November 2004, Nagano, Japan, International Sports Science Network Forum: Exercise and Cytokines.

### **Research area 4.**

Stefanos Volianitis:

“Arm blood flow and oxygen uptake in trained and untrained man”. Forolympisk symposium Athen, August 2004.

### **Research area 5.**

John Vissing:

3.6.2004: Invited speaker at the Scandinavian Congress of Neurology, Falkonercentret, Frederiksberg, (genetics in mitochondrial diseases).

4.7.2004: Invited speaker at EUROMIT 6, Nijmegen, Holland (training of patients with mitochondrial diseases).

13.11.2004: Inviteret foredragsholder ved Dansk Selskab for Klinisk Genetik, omhandlende Dystrofia myotonica. Vejle, Vejle.

### **Research area 6.**

Michael Kjær:

“How does ageing muscle react to exercise?”. German Sports Medicine Society Congress, Freiburg, Germany, March 2004.

“Physiology of tendon in exercise” Scandinavian Congress of Sports Medicine, Stockholm, Sweden, March 2004

“Physiological changes in tendon tissue with mechanical loading” American College of Sports Medicine Congress, Indianapolis, USA, June 2004.

“Functional adaptation to loading in musculo-skeletal tissue in humans” Journal of Physiology Conference, Nottingham, England, July 2004

“Exercise and counteracting musculoskeletal disorders” European Society of Occupational Medicine Congress, Zürich, Schweiz, July 2004.

“Muscle loss in ageing – effect of training on functional capacity” European Society for Geriatrics Congress, Wien, Austria, Sept 2004.

“Sarkopenia – counteracting muscle loss in ageing” Annual Congress of Norwegian Society for Sports Medicine. Harstad, Norway, Nov 2004.

Henning Langberg:

“Use of microdialysis to study changes in connective tissue”, European Connective Tissue Society Congress, Taormina, Italy, July 2004.

“Adaption of human tendon to loading”, European Congress for Physiotherapy, Lisbon, Portugal, October 2004.

Peter Magnusson:

“Tendon properties in humans”, European College of Sports Sciences, Clermont Ferrand, France, July 2004.

## **Editorial tasks, memberships of international scientific committees, and advanced academic evaluation.**

Flemming Dela. Member of the International Research Group on Biochemistry of Exercise.

Henrik Galbo. Member of Editorial Board at Int J Sports Med and of Advisory Board at Scand J Med Sci Sports.

Henrik Galbo. Member of the International Research Group on Biochemistry of Exercise.

Carsten Juel. Member of Editorial Board at Eur. J Appl. Physiol.

Michael Kjær. Editor-in-Chief (Scand J Med Sci Sports), Editor (J Physiol), Editorial board (Eur J Appl Physiol, Clin Physiol).

Peter Magnusson. Section editor (Scand J Med Sci Sports).

Bente Klarlund Pedersen. Associate Editor at Pflügers Archiv/Eur J Physiol Exp Physiol and member of Editorial board at Eur J Appl Physiol og Exerc Immunol Rev.

Bente Klarlund Pedersen. Evaluated doctoral thesis: Eirunn Knudsen, Oslo: Ecotaxis (“homing”) of leukocytes in the healthy and inflamed rat.

Bente Klarlund Pedersen. Evaluated PhD-thesis: Graeme Iain Lancaster, University of Birmingham, UK: The influence of exercise on novel aspects of the immune system.

Bente Klarlund Pedersen. Chairman of board of evaluation for senior group leader and junior group leader at BRIC.

Bente Klarlund Pedersen. October 2004 University of Columbia-Missouri. Site visit, served on an External Review Team (ERT), who visited the University of Missouri at Columbia (MU) to review the merits of formalizing a Human Activity Center (HAC) for Research.

Erik A. Richter. Member of Editorial Board Diabetes.

Erik A. Richter. Expert evaluator of a candidate for promotion to Associate Professor, Yale University, USA.

Erik A. Richer. Expert evaluator of a candidate for promotion to University Professor, Toronto University, Canada.

Erik A. Richter. Expert evaluator of a candidate for receiving „Speciel academic recognition“ at University of California, Los Angeles, USA.

Erik A. Richter. Grant-reviewer for Science Foundation of Ireland, Basic Sciences.

N. H. Secher. Editor ved Eur J Appl Physiol. og Exp Physiol.

N. H. Secher. Bedømt ph.d.-afhandlingen: Berit Thornvig Jensen: Physiological and patophysiological aspects of QT dynamics. Sundhedsvidenskabeligt Fakultet, University of Copenhagen, 08.10. 2004.

John Vissing. Member of European Neuromuscular Center's Research Committee

## Symposia and PhD courses arranged by CMRC

### **Research area 5.**

John Vissing co-organizer of and chairman at The 35th Scandinavian Neurological Society Congress, Falkonercentret, Frederiksberg, April 2004.

### **Research area 6.**

Kursus i arbejdsfysiologi og idrætsmedicin. Københavns Universitet. Afholdtes på BBH. 22.-26.11. 2004.

Arranged the CMRC symposium 6th BBH symposium on Sports Medicine. 19 – 21 August, Carlsberg Academy, "Extracellular matrix – conversion of mechanical loading into functional adaptation".

## Seminars

18.03. 2004 The August Krogh Institute. "Physical activity and the interaction between muscle and connective tissue".

15.04. 2004 The August Krogh Institute. "Newer peptide hormones/interorgan signalling molecules".

06.05. 2004 The August Krogh Institute. CMRC Youngsters international seminar: "Youngster activities within the 4 Universities Exercise Science Collaboration".

13.05. 2004 The August Krogh Institute. "The brain at work: Central and peripheral limitations to exercise".

18.06. 2004 Panum Institute. Contributions Clermont-Ferrand. CMRC-Presentations for the Eur. College of Sports Science's Congress in Clermont-Ferrand 2004.

23.08. 2004 Bispebjerg Hospital. "Physiological and pathological adaptation of skeletal muscle".

29.09. 2004 Rigshospitalet. "Regulation and effects of ions in contracting muscle".

21.10. 2004 Rigshospitalet. "Role of intact mitochondrial metabolism for training effects, oxidative capacity and blood flow regulation".

11.11. 2004 The August Krogh Institute. "AMPK, malonyl CoA and disease in humans".