

CMRC Annual Report, 2005

Results obtained

Research Area 1. Regulation of carbohydrate and fat metabolism. Association with insulin sensitivity/resistance and type 2 diabetes.

It is thought that the high blood glucose concentration in patients with type 2 diabetes contributes to or, in fact, is the cause of an increase in the production of reactive oxygen species (ROS) e.g. in skeletal muscle. A number of antioxidant systems protects against ROS. We have shown that the concentration of one of these, metallothionein, is reduced in plasma and skeletal muscle in patients with type 2 diabetes. The increased ROS production in the patients might reflect impaired mitochondrial function. We have studied this possibility using "high resolution spirometry" in skeletal muscle. We found that the maximum oxygen flux is reduced in the patients, and that the defect is localized to complex 1 and/or 2 in the respiratory chain of the mitochondria. We have carried out similar studies on patients with polycystic ovarian syndrome, who are insulin resistant but without significant hyperglycemia. We found that insulin resistance per se does not cause impairment of mitochondrial function, but that this is seen if insulin resistance is accompanied by obesity.

People with impaired glucose tolerance (IGT) are moderately insulin resistant. We have studied whether in subjects with IGT the effect of combined exercise and hyperinsulinemia on glucose uptake in muscle is also reduced. On the opposite, glucose uptake in response to the combined stimulus was increased compared to findings in healthy subjects. This could not be explained by differences in muscle glycogen content.

It has been known for about 20 years that a single bout of exercise increases the insulin sensitivity of the muscles involved for hours postexercise. The molecular mechanism explaining this phenomenon has not been revealed despite much research. We have now shown that a single bout of exercise increases the activity of insulin receptor substrate 2 associated phosphatidylinositol 3-phosphokinase (IRS2 associated PI3-K) as well as the sensitivity of atypical protein kinase C isoforms (aPKC) for the product of the PI3-K reaction, phosphatidylinositol-3,4,5-triphosphate (PIP3). Both these reactions are part of the insulin signaling cascade, and the results show for the first time that physical activity directly influences and enhances insulin signaling.

The effect of intermittent fasting (every other day in 2 wks) on insulin mediated glucose uptake has been studied in healthy young men. The idea was to mimic the oscillations in energy depots accompanying physically training, during which the effect of insulin increases. We found that intermittent fasting enhances insulin action on both glucose uptake from plasma and lipolysis. The concentrations of adiponectin in plasma were increased and this may to some extent explain the described effects of fasting on insulin action.

Training increases the effect of insulin on muscle glucose uptake in patients with type 2 diabetes. However, it is not known if the necessary training on a given day has to be carried out as one continuous bout or if the effect of exercise periods can be accumulated over the day. Accordingly, we compared effects on glucose tolerance of 4 wks of training consisting in 1x30 min or 3x10 min, respectively, isocaloric training per day in patients with type 2 diabetes. Our results indicate that the benefit of repeated daily exercise periods is higher than that of one continuous exercise session per day.

We have shown that regularly repeated, long lasting, low intensity whole body exercise induces different adaptive responses in arms and legs, respectively. Thus, the increase in glucose transporters in muscle is particularly pronounced in the arms.

In young, healthy men we have studied the effect of caffeine on endogenous glucose production (EGP) and insulin mediated tissue glucose uptake. Caffeine did not influence EGP but impaired glucose uptake, an effect which in part could be attributed to increases in plasma epinephrine concentrations.

Chemical activation of the AMP dependent protein kinase (AMPK) mediates a number of physiological changes in contracting muscle, e.g. regulation of glucose uptake and oxidation, lipid oxidation, insulin sensitivity as well as of several genes. By using genetically modified rodents we elucidate causal relationships between AMPK and biological effects primarily seen in response to exercise. Because AMPK is a heterotrimeric protein with 7 isoforms of the subunits, it is theoretically possible to form 12 different AMPK complexes. In order to understand the role of AMPK we have characterized the AMPK complexes present in human muscle. We have found 3 of the 12 possible 5`AMP-dependent protein kinase (AMPK) heterotrimeric complexes in human muscle. Apparently, they are not changed in muscle from type 2 diabetic patients, nor are they changed by acute exercise. However, training changes the composition of the complexes.

A number of AMPK stimuli increase glucose transport in resting skeletal muscle, and we have previously demonstrated a causal relationship between AMPK and glucose transport at rest. The exact mechanism by which AMPK regulates transport is not known in detail, but translocation of the glucose transporting protein GLUT4 is involved. The GAP protein AS160 regulates the GTPase activity of several Rab proteins and has been shown to be essential for insulin stimulated GLUT4 translocation and glucose transport in adipocytes. Using 3 different genetically modified mouse models, which do not express one or more of the AMPK subunits, we have identified AS160 as a substrate for AMPK in resting as well as in contracting muscle. Whether AS160 plays a role in AMPK induced glucose transport is not known yet.

Using the genetically modified rodent models we have also shown that AMPK in resting muscle regulates several genes coding for metabolic enzymes. Nevertheless, our studies indicate that the activation of AMPK elicited by muscle contraction is not necessary for the gene activation seen in response to exercise.

During exercise glucose transporting proteins (GLUT4) are translocated from intramyocellular stores to the sarcolemma, and, in turn, muscle glucose uptake from the blood is increased. The molecular signals involved in this GLUT4 translocation are still largely unknown, but focus is on a few enzymes activated by contractions. We have in the past year studied the importance of the enzymes AMPK and Calcium/calmodulin kinase (CaMK). We have used both transgenic mice, which do not express AMPK, and various pharmacological inhibitors of CaMK. Our studies have clearly shown that lack of AMPK activity in muscle reduces glucose uptake in working muscle. Also CaMK inhibitors reduce glucose uptake in working muscle. And so do blockers of the "upstream" kinase of CaMK, CaMK-kinase (CaMKK). Interestingly, there is no additive effect of simultaneous blockade of the two enzyme systems. This indicates that the two signaling pathways act in series, rather than in parallel. In line with this interpretation, we have shown that CaMKK is an upstream activator also of AMPK in skeletal muscle.

The activation of the various isoforms of CaMK has been studied in muscle from rat and man. CaMKII is activated at onset of exercise and the activation lasts throughout exercise and vanishes rapidly, when exercise stops. CaMKIII is also activated immediately at onset of exercise, and we have shown that this isoform phosphorylates and, in turn, inhibits the activity of eucariotic elongation factor 2 (eEF2), thereby inhibiting protein synthesis. It is known that protein synthesis is decreased during exercise, but the molecular mechanism responsible for this has not been known. An important step in mRNA translation is elongation of the peptide chain, which finally becomes the complete protein. The elongation requires interference of eEF2, but this is efficiently impaired by phosphorylation of eEF2. Thus, phosphorylation of eEF2 is a quick and reversible way of impeding protein synthesis. Because peptide elongation is quite energy consuming, it is expedient that during exercise this process is transiently stopped thereby saving energy for the contraction process. Interestingly, during 90 min exercise the activity of the mitochondrial enzyme citrate synthase increases in women but not in men. One possibility is that this reflects a gender difference in synthesis of the enzyme protein, which again might reflect a lower phosphorylation of eEF2 in muscle in women compared with men.

We have shown that diffusion through the t-tubules serves to transport hormones and nutrients from plasma to the interior of muscle cells. In contrast to previous beliefs, a major part of insulin activated PI3-kinase is also situated in the t-tubule membranes and not in the sarcolemma. Using confocal fluorescence microscopy on muscle cells in situ in anesthetized mice we have studied insulin mediated PI3-kinase activation and GLUT4 translocation in two conditions accompanied by insulin resistance: Denervation and prolonged intake of a high-fat diet. In denervated muscle the insulin mediated PI3-kinase activation in t-tubule membranes is nearly completely abolished, whereas the PI3-kinase activation is markedly increased (50%) in sarcolemma. Correspondingly, the GLUT4 translocation to t-tubules is also markedly reduced, whereas the translocation to

sarcolemma is normal. In mice that have been on a high-fat diet for 12 wks PI3-kinase activation is reduced by 60% in t-tubules, whereas it is only reduced 25% in sarcolemma. These findings demonstrate a defective insulin signaling in insulin resistant states and, furthermore, point at an important role of t-tubules in the development of insulin resistance.

By detailed microscopy of GLUT4 vesicle movements upon stimulation with insulin we have shown that GLUT4 stores in muscle are recruited only to local membrane surfaces, e.g. to t-tubules. So, GLUT4 vesicles do not move over longer distances, e.g. from the interior of muscle cells to the sarcolemma, as it is the case in e.g. adipocytes.

The activity of the enzyme glycogen synthase (GS) is diminished in muscle of type 2 diabetes patients, a fact contributing to their insulin resistance. The activity of GS is regulated by phosphorylation. In addition to this, we have now shown that after glycogen depleting exercise in healthy rats and rabbits glycogen resynthesis in muscle is accompanied by translocation of GS from the cytosol to a "new" dynamic cellular organelle, a glycosoma. The translocation of GS depends on phosphorylation and formation of glycosomas requires remodeling of the actin skeleton.

The insulin sensitivity of middle-aged men and women subjected to i.v. intralipid infusion has been studied. Preliminary results indicate that intralipid reduces insulin mediated glucose uptake in both men and women.

Decreased peripheral insulin action increases the risk of type 2 diabetes. Insulin action in muscle is influenced by the metabolic conditions within and around the muscle cells. Several studies have shown a relationship between fat metabolism and insulin action. More than 40% of HIV positive patients in highly active anti-retroviral therapy (HAART) develop a fat redistribution syndrome with loss of peripheral adipose tissue. This is accompanied by reduced peripheral insulin action, primarily reduced insulin mediated non-oxidative glucose metabolism, i.e. glycogen storage. We have now identified defects in the insulin-signaling cascade in patients with HIV-associated adipose tissue dystrophy: In Akt, GSK-3 and GS. We also found an inverse correlation between the plasma lipid content in the patients and the insulin mediated activity of GS. Studies on cell cultures indicate that this reflects a cause and effect relationship.

Skeletal muscle cells contain a triglyceride store in lipid droplets localized in the cytosol. This is an important energy store that can be mobilized by both catecholamines and contractions. We have previously shown that it is most likely that the enzyme Hormone-sensitive Lipase (HSL) accounts for the mobilization of triglyceride in muscle cells as it is the case in adipocytes. To further elucidate the role of HSL in skeletal muscle we have studied soleus muscles of HSL knockout/null mice with transcriptome and proteome analyses. We found an upregulation on the mRNA level of fructose-1,6 bisphosphatase, fructose-2,6-bisphosphatase and phosphorylase kinase gamma 1A indicating an increased glycogen flux. Furthermore, the HSL-null mice had increased levels of intramyocellular triglyceride indicating that HSL is important for triglyceride breakdown in skeletal muscle.

We have studied the influence of prolonged exercise on intramyocellular triglyceride. We found that during 2 hours of ergometer cycling triglyceride depletion predominantly takes place in oxidative type II fibres, and that the depletion is nearly abolished if subjects are given carbohydrate during exercise. The exact regulation of HSL in exercising muscle is not known. We have used antibodies against the 5 different phosphorylation sites of HSL to elucidate, whether the state of phosphorylation is changed by exercise and may account for the change in HSL activity.

Acute physical activity increases blood flow and lipolysis in adipose tissue. However, it is not known, whether during exercise blood flow and lipolysis are higher in adipose tissue adjacent to working muscle compared with adipose tissue adjacent to resting muscle. We studied young, healthy men, who carried out one-legged exercise at three intensities. We found that both blood flow and lipolysis were higher in adipose tissue above the working muscles than in adipose tissue above resting muscle in the non-exercising leg. These findings indicate that the size of selected adipose tissues can be specifically reduced by training.

The prevalence of extreme obesity is increasing. We have studied the effect of 15 wks of life style intervention consisting in diet and 2-3 hours of daily physical activity in 27 obese (BMI=44±1 kg/m²) subjects of both genders. The intervention resulted in a reduction in body mass of 14 kg and in fat mass of 4%. Maximum

oxygen uptake per kg increased 25% and total cholesterol in plasma decreased 8%. Also oral glucose tolerance was improved. The study showed that life style intervention is possible and can improve health also in extremely obese patients.

We have studied the effect of substrate availability after exercise on the genes coding for metabolic enzymes in skeletal muscle. We found an enhanced transcription of genes coding for enzymes involved in fat metabolism, when after exercise meals were high in fat rather than in carbohydrate.

Several metabolic genes are activated early after exercise, but this is not so for mitochondrial genes although regularly repeated exercise (training) results in increased expression of these genes on both the mRNA and the protein level. We have studied the regulation of the mitochondrial genes late in the recovery period after exercise. It was found that mRNA levels of several mitochondrial genes are elevated 14-18 hours after exercise.

Peroxisome proliferator activated receptor γ co-activator-1 α (PGC-1 α) is a transcriptional co-activator apparently of big importance for mitochondrial biogenesis and regulation of several metabolic proteins. We have previously shown that contraction increases the transcription and mRNA levels of PGC-1 α in skeletal muscle. Now we have studied the role of calcium for the regulation of the gene in muscle cell cultures. We found that calcium markedly increases the mRNA levels of both PGC-1 α and hexokinase 11, and this regulation involves calcineurin.

We have compared two isoforms of PGC-1 (alpha and beta) by transfecting muscle cell cultures with DNA and overexpressing either of the two isoforms. We found that the two isoforms have very similar impact on many metabolic and contractile genes. However, a few differences exist, e.g. a higher induction of MHC11A by PGC-1 beta and a higher potential for glycogen storage by PGC-1 alpha over expression.

Free oxygen radicals and NO have been proposed to be involved in regulation of gene expression. In order to study this in skeletal muscle we have treated cells with pro- and antioxidants. We found that antioxidants abolish the contraction induced increase in some metabolic genes. Correspondingly, incubation of cells with pro-oxidants resulted in increased mRNA levels of these genes upon contraction. Furthermore, using the microdialysis technique in muscle in exercising humans, we have directly shown that free oxygen radicals are produced in muscle and that the rate of production is directly related to exercise intensity.

We have applied siRNA transfection of muscle cell cultures and shown that we are able to block creatine kinase mRNA and activity by this technique.

Finally, we have studied the potential exercise-induced regulation of metabolic genes in human adipose tissue. Within 2 hours of recovery after exercise only changes in visfatin mRNA and in PPAR delta mRNA were found.

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

We have found an exercise-induced increase in mRNA levels of the subunits of the Na⁺,K⁺ pump in human skeletal muscle. This indicates that the increase in concentration of this pump after training reflects transcriptional activation. Furthermore, we have shown that it is probably a locally generated signal from the muscle cell that elicits an increase in Na⁺,K⁺ pump mRNA, because this increase does not vary with the mass of working muscle. Finally, we have shown that two different muscles (the deltoid and the vastus lateralis, respectively) respond to a different extent to dexamethasone, which increases the Na⁺,K⁺ pump content in both muscles.

We have localized the channels and transport proteins involved in K⁺ fluxes from muscle cells to interstitial fluid and plasma during exercise. The ATP sensitive K⁺ channel and the Na⁺-K⁺-2Cl⁻ co-transporter are predominantly located in sarcolemma, while the Kir2.1 channel and the Ca⁺⁺dependent K⁺ channel predominantly are located in the t-tubules. By administration of citrate and use of microdialysis we have shown that alkalosis reduces interstitial K⁺ accumulation in working muscle, a fact which may help explain the effect of

pH on development of fatigue. In contrast to these findings, it has recently surprisingly been claimed that lactic acid enhances endurance of muscle. However, in accordance with previous findings we find that lactic acid impairs endurance.

We have completed experiments elucidating the role of plasma K⁺ for regulation of the peripheral circulation. Infusion of potassium to an arterial concentration similar to that seen during exercise increased blood flow. The effect was accounted for by activation of barium-sensitive unidirectional K⁺ channels in vascular smooth muscle cells. We have also shown that injection of NESP (EPO) in humans increases the density of several transport proteins in the plasma membrane of red blood cells, indicating that NESP in addition to increasing the number of erythrocytes also increases the quality of these cells.

We have found that passive heating of thigh muscle from 35 to 38°C does not influence oxygen uptake nor mechanical efficiency during dynamic one-leg kicking exercise. On the other hand, our studies show that the number and type of muscle fibres involved in exercise is important for energy utilization during dynamic exercise. Thus, after prior glycogen depletion of fast twitch fibres more fast twitch fibres will be recruited for a given moderate work load, and this increase in number of active muscle fibres will be accompanied by a higher pulmonary oxygen uptake and a lower mechanical efficiency during the work. Furthermore, preliminary data indicate that inhibition of recruitment of slow twitch fibres by the neuromuscular blocker Nimbex increases oxygen uptake during dynamic one-legged exercise at low and moderate submaximal exercise intensities. We have also shown that in the beginning of dynamic exercise there is an increase in concentration of intermediary substances in the Krebs Cycle, but this expansion is not necessary for an increase in mitochondrial respiration.

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

Fat cells secrete hormones called adipokines. We have measured interstitial concentrations and mRNA for the adipokines adiponectin and IL-6 in subcutaneous, abdominal adipose tissue in lean and obese young men before and after 60 min of exercise at 55% of maximal oxygen uptake. The interstitial concentration of adiponectin was higher in lean than in obese subjects and increased by 100% in both groups during exercise, while the plasma concentration did not increase. Adiponectin mRNA in adipose tissue did not differ between groups and also did not change with exercise. Surprisingly, at rest the interstitial adiponectin concentration was 5 times lower than the concentration in plasma. Interstitial and plasma IL-6 concentrations did not differ between lean and obese subjects, but both these variables and IL-6 mRNA concentrations in adipose tissue increased during and after exercise. So, the study shows that exercise increases the interstitial concentration of at least two adipokines in subcutaneous, abdominal adipose tissue.

Obesity is accompanied by “low-grade inflammation”, which may be one of the mechanisms explaining the insulin resistance seen in obese people. We have studied the influence of life style intervention for 15 wks (see Research area 1) on inflammatory markers in plasma and adipose and muscle tissue in 27 extremely obese subjects. After the intervention we found lower concentrations of the inflammatory markers IL-6, IL-8, CRP and MCP-1 and a reduced expression in adipose tissue of IL-6, IL-8, TNF- α and the macrophage markers CD14 and CD68. In muscle we found no sign of inflammation either before or after the intervention. Life style intervention increased the concentration in plasma and the expression in adipose tissue of the anti-inflammatory hormone adiponectin, while the expression of adiponectin receptors was changed neither in adipose nor in muscle tissue. The main conclusion is that life style intervention can inhibit “low-grade inflammation” in plasma and adipose tissue in extremely obese subjects.

We have started a systematic mapping of adipokine and myokine production from adipose and muscle tissue, respectively. Using 2D-protein electrophoresis we have found that stimulation with insulin doubles the secretion of proteins from collagenase isolated rat fat cells. With the same method we have found that contraction doubles the secretion of peptides from incubated rat muscles.

We have previously shown that muscle cells during contractions release the cytokine IL-6. We have now shown that also the cytokine IL-8 is a myokine. We have proposed that IL-8 is involved in exercise-induced angiogenesis. We have found that the receptors of both IL-6 and IL-8 are up regulated in muscle by exercise. TNF- α is a highly proinflammatory cytokine. We have shown that TNF- α induces peripheral insulin resistance in

man and localized its point of attack in the insulin signaling cascade. Finally, we have found that the cytokine IL-18 is associated with insulin resistance and that this cytokine is expressed in both adipose tissue and type 2 muscle fibres in man.

Research area 4. Central and peripheral circulation.

The factors limiting circulatory capacity has been studied during maximal exercise. We have again shown that muscle blood flow is higher when a muscle group works alone, e.g. during leg kicking, than when it participates in whole body exercise. We have now shown that this reflects that during whole body exercise the increase in cardiac output is not high enough to produce the blood pressure, which the baroreceptors are set to control. Accordingly, vasoconstriction is elicited both in the working muscles and in the brain. The studies also indicate that cardiac output is limited by the venous return from working muscles. We have shown that during hypoxia the influence of the parasympathetic nerve system (n.vagus) on exercise heart rate is markedly increased. This explains that during exercise at high altitude maximal heart rate is reduced. We have also shown that maximal aerobic work capacity is identical for arms and leg in inuits (original inhabitants of Greenland), whereas it is 40% lower in arms than in legs in Danes.

Brain blood flow has been studied to explore which brain areas are important for the increases in heart rate and blood pressure seen during exercise. In paraplegics, who are paralyzed in the legs, we have shown that heart rate and blood pressure increase, when the patients try to move the legs, and that this effort is accompanied by activation of the insula area in the brain.

We have also shown that the brain takes up ammonia from plasma during exercise. This fact may explain why auto regulation of brain blood flow becomes less precise during exercise. Furthermore, this uptake of ammonia indicates that the activated brain produces aminoacids, which may be used in formation of neurotransmitters. In earlier studies we have shown that VEGF (vascular endothelial growth factor) is released from muscle and that VEGF mRNA increases in contracting muscle cells. We have now added to this by demonstrating in vitro an interaction between endothelium cells and skeletal muscle cells: Contracting muscle cells release a substance, which induces an increase in VEGF mRNA in endothelium cells. Studies of the coupling between the transcription factor Hypoxia-inducible factor 1 α (HIF-1 α) and EGVF have shown that the contraction induced increase in VEGF mRNA is not dependent on hypoxia in muscle cells in culture.

Insulin resistance includes insulin mediated vasodilatation. We have studied the effect of stimulation with acetylcholine, adenosine and nitroglycerine, respectively, with and without hyperinsulinemia (endothelium dependent and independent vasodilatation) in the forearm of patients with type 2 diabetes and healthy controls. Endothelium dependent vasodilatation was diminished in the patients. Furthermore, during maximal blood flow stimulation a-v glucose extraction decreased markedly in the patients but not in the controls. This finding emphasizes that in type 2 diabetes the main problem is diminished ability to extract glucose from blood, not an impaired supply of glucose to muscle.

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

From previous studies it is known that patients with lack of the enzyme AMP deaminase in skeletal muscle has an increased production of adenosine in muscle. To clarify the mechanism we have studied the importance of AMP 5' nucleotidase in patients, who lack AMP deaminase. The results showed that the increased production of adenosine in these patients was due to an increased availability of substrate for the AMP 5' nucleotidase without any change in activity of the enzyme.

Fat metabolism has been studied in patients with myophosphorylase deficiency and, in turn, impaired carbohydrate metabolism. It has been assumed that these patients would show an enhanced fat oxidation during exercise. However, our studies including stable isotopes and either blockers of fat metabolism or administration of free fatty acids have shown that fat metabolism is not increased in these patients. The studies have increased our knowledge about the metabolism in these patients and, furthermore, points to the necessity in general of an intact carbohydrate metabolism for fat combustion.

Molecular subgrouping of patients with limb girdle muscle dystrophy has been done in a national investigation. It was found that a defect in the gene coding for fukutin-related protein (FKRP) is much more frequent in Denmark (exists in 40% of the patients) than in the rest of the world. We are now developing a knock-out and a knock-in mouse model of the disease to further explore the pathogenesis.

We have disproved the previous assumption that the correlation between geno- and phenotype is poor in patients with mitochondrial diseases. Our studies show a good correlation when phenotype and type and load of mutations, respectively, are compared in the same tissues. Moreover, we have shown that the reason why the load of mutations in mitochondria varies between tissues is a postnatal, tissue specific modulation of the presence of mutations.

Research area 6. Interaction between muscle and connective tissue. Relationship with everyday activities.

We have further described the exercise-induced increase in protein synthesis in both intramuscular connective tissue and tendon. The increase in collagen synthesis is much in agreement with these findings the in vitro tensile strength of female tendons is lower than that of male tendons. Our findings support the conclusion that the connective tissue in tendons and muscle adapts more slowly in women than in men, and this fits with the fact that women have a higher incidence of overloading injuries of connective tissue than men.

We have carried out biomechanical measurements of the mechanical compliance of tendons. Within a given tendon marked regional differences were found. Thus, the deep parts of the patella tendon are less resistant to mechanical stress and break at a lower load than the anterior parts of the tendon. This explains that the overloading injuries of the patella tendon seen in the clinic are always located in the posterior part of the tendon.

We have shown that muscle work elicits a marked mRNA expression of various growth factors and matrix proteins in the involved tendons. Similar changes are found in muscle biopsies indicating a close coupling of exercise-induced events in muscle and tendons during exercise.

We have compared intense voluntary eccentric exercise with electrically induced exercise. We found that even at very heavy eccentric exercise it is particularly the intramuscular connective tissue that is damaged, while there is some damage of the cytoskeleton of the muscle fibres but nearly no damage of the remaining components of the fibres including the sarcolemma. In contrast, electrostimulation results in a marked destruction of the muscle cells. Only where muscle cells are damaged is formation of new satellite cells seen. In this context it is interesting to note that we in elderly healthy subjects, who complete a muscle training program, find an activation and increase in number of satellite cells along with the development of muscle hypertrophy, which is comparable to findings in young subjects. There is no gender difference in this adaptation.

We have isolated satellite cells from fast and slow muscles, respectively, and shown that they differentiate to muscle fibres with different metabolic and contractile phenotypes. So, satellite cells apparently have a memory for their origin.

Studies of neck muscles from patients with long lasting neck and shoulder pain have shown increased concentrations of nociceptive substances like serotonin, glutamine and potassium both at rest and during moderate work, and these findings correlate with pain intensity.

The influence of prostaglandins and NO on blood flow in muscle and connective tissue has been studied by PET-scanning. We found that local administration of prostaglandin and NO blockers in muscle changed the regional blood flow without interfering with glucose uptake.

We have studied the influence of testosterone during strength training by pharmacological blockade of testosterone production in humans. The study showed that testosterone blockade inhibits an increase in

muscle mass and abolishes an increase in strength. The induction of the muscle transcription factor myogenin does not depend on testosterone.

We have previously shown that strength training followed by detraining is a good model to induce marked and transient hypertrophy of human muscle. We have now demonstrated a decrease in the level of mRNA for the anti-growth factor myostatin during the training period and a subsequent increase during detraining. This indicates that myostatin regulates muscle fibre size. We have established a western blotting assay for analysis of myostatin protein. Preliminary data indicate that myostatin protein changes in parallel with the mentioned mRNA measurements. We have injected myostatin in rats to find the target genes for myostatin signaling in muscle. Using microarrays we have identified candidate genes.

Subjects with acquired brain damage, e.g. resulting from trauma, hemorrhage, hypoxia, tumor or infection, often develop hemiparesis. Traditional physiotherapy may ameliorate impaired coordination, but does not increase strength of the affected leg. We have shown that an extensive program of strength and endurance training initiate considerable fibre type shift and hypertrophy as well as increased capillarisation and mitochondrial mass. These changes imply reduced risk of metabolic syndrome.

Chronic uremia causes abnormalities in skeletal muscle, changes in metabolism and lowered work capacity. We have shown that uremia is accompanied by a very marked reduction in the proportion of type 1 fibres and an increase in the proportion of type 2x fibres in skeletal muscle. These changes far exceed what can be explained by the physical inactivity associated with uremia. Surprisingly, the muscle fibres do not atrophy to any significant extent. So, our findings indicate that in uremia the metabolic disturbances can elicit a marked reduction of type 1 muscle fibres.

Publications

Research area 1.

PhD-theses

Sebastian Beck Jørgensen: The role of AMPK in regulation of glucose metabolism and expression of metabolic genes and proteins in skeletal muscle. University of Copenhagen, 15.11.05.

Massimo Sacchetti: "Skeletal muscle fatty acid kinetics in healthy individuals and type 2 diabetic patients", University of Copenhagen, July 2005.

Papers in accordance with the CMRC research strategy

Andersson U, Treebak JT, Nielsen JN, Smith KL, Abbott CR, Small CJ, Carling D and Richter EA. Exercise in rats does not alter hypothalamic AMP-activated protein kinase activity. *Biochem Biophys Res Commun* 329: 719-725, 2005.

Batram DS, Graham TE, Richter EA, & Dela F (2005). The effect of caffeine on glucose kinetics in humans- influence of adrenaline. *J Physiol* 2005, 569: 347-55.

De Bock K, Richter EA, Russell AP, Eijnde BO, Derave W, Ramaekers M, Koninckx E, Leger B, Verhaeghe J and Hespel P. Exercise in the fasted state facilitates fibre type-specific intramyocellular lipid breakdown and stimulates glycogen resynthesis in humans. *J Physiol* 564: 649-660, 2005.

Colombo M, Agger A, Gregersen S, Jeppesen PB, Xiao J, Abdula R, Kruhoffer M, Orntoft T, Ploug T, Galbo H, and Hermansen K: Prevention of hyperglycemia in diabetic ZDF rats by exercise training: Effects on gene expression in insulin sensitive tissues determined by high-density oligonucleotide microarray analysis. (2005), *Metabolism*, in press.

Donsmark M, Langfort J, Holm C, Ploug T, & Galbo H. Hormone-sensitive lipase as mediator of lipolysis in contracting skeletal muscle. *Exerc Sport Sci Rev* 33, 127-133, 2005.

Eijnde BO, Derave W, Wojtaszewski JF, Richter EA and Hespel P. AMP kinase expression and activity in human skeletal muscle: effects of immobilization, retraining, and creatine supplementation. *J Appl Physiol* 98:1228-1233, 2005. Halberg N, M. Henriksen, N. Soderhamn, B. Stalknecht, T. Ploug, P. Schjerling, and F. Dela. The effect of intermittent fasting and re-feeding on insulin action in healthy men. *J Appl Physiol*, 99:2128-2136, 2005.

Hansson O, Donsmark M, Ling C, Nevsten P, Danfelter M, Andersen JL, Galbo H, and Holm C. Transcriptome and proteome analysis of soleus muscle of hormone-sensitive lipase-null mice. *Journal of Lipid Research*, 46, 2614-2623, 2005.

Jensen CB, Storgaard H, Holst JJ, Dela F, Madsbad S, & Vaag A. Young, low-birth-weight men are not more susceptible to the diabetogenic effects of a prolonged free fatty acid exposure than matched controls. *Metabolism* 54, 1398-1406, 2005.

Jorgensen S.B., J.F. Wojtaszewski, B. Viollet, F. Andreelli, J.B. Birk, Y. Hellsten, P. Schjerling, S. Vaulont, P.D. Neuffer, E.A. Richter, H. Pilegaard. Effects of alpha-AMPK knockout on exercise-induced gene activation in mouse skeletal muscle. *FASEB J.* 19:1146-8, 2005.

Lundby C, Gassman, M, Pilegaard H. Regular endurance training reduces the exercise induced HIF-1alpha and HIF-2alpha mRNA expression in human skeletal muscle in normoxic conditions. *Eur J Appl Physiol* 12; 1-7, 2005.

Lundby C, Nordsborg, N, Kusuvara K, Kristensen KM, Neuffer PD, Pilegaard H. Gene expression in human skeletal muscle: alternative normalization method and effect of repeated biopsies. *Eur J Appl Physiol* 95:351-60, 2005.

Marcuello A, Gonzalez-Alonso J, Calbet JA, Damsgaard R, Lopez-Perez MJ, Sanchez C. Skeletal muscle mitochondrial DNA content in exercising humans. *J Appl Physiol* 99(4):1372-1377, 2005.

Olsen DB, Sacchetti M, Dela F, Ploug T, & Saltin B. Glucose clearance is higher in arm than leg muscle in type 2 diabetes. *J Physiol* 565, 555-562, 2005.

Nordby P, Saltin B and Helge JW. (2005) Whole body peak fat oxidation determined by graded exercise: a relation to muscle oxidative capacity. *Scand J Sports Med*. In press.

Pilegaard H, Osada T, Andersen LT, Helge JW, Saltin B, & Neuffer PD. Substrate availability and transcriptional regulation of metabolic genes in human skeletal muscle during recovery from exercise. *Metabolism* 54, 1048-1055, 2005.

Poulsen P, Wojtaszewski JF, Petersen I, Christensen K, Richter EA, Beck-Nielsen H and Vaag A. Impact of genetic versus environmental factors on the control of muscle glycogen synthase activation in twins. *Diabetes* 54: 1289-1296, 2005.

Prats C, Cadefau JA, Cusso R, Qvortrup K, Nielsen JN, Wojtaszewski JF, Hardie DG, Stewart G, Hansen BF, & Ploug T. Phosphorylation-dependent translocation of glycogen synthase to a novel structure during glycogen resynthesis. *J Biol Chem* 280, 23165-23172, 2005.

Roepstorff C, Halberg N, Hillig T, Saha AK, Ruderman NB, Wojtaszewski JF, Richter EA, & Kiens B. Malonyl-CoA and carnitine in regulation of fat oxidation in human skeletal muscle during exercise. *Am J Physiol*, 288, E133-E142, 2005.

Roepstorff C., P. Schjerling, B. Vistisen, M. Madsen, C.H. Steffensen, M.H. Rider, B. Kiens. Regulation of oxidative enzyme activity and eukaryotic elongation factor 2 in human skeletal muscle: influence of gender and exercise. *Acta Physiol Scand*, 184:215-24, 2005.

Roepstorff C, Vistisen B and Kiens B. Intramuscular Triacylglycerol in Energy Metabolism during Exercise in Humans. *Exerc Sport Sci Rev* 33:182-188, 2005.

Rose AJ, Broholm C, Kiillerich K, Finn SG, Proud CG, Rider MH, Richter EA and Kiens B. Exercise rapidly increases eukaryotic elongation factor 2 phosphorylation in skeletal muscle of men. *J Physiol* 569: 233-8, 2005.

Rose AJ and Richter EA. Skeletal muscle glucose uptake during exercise: how is it regulated? *Physiology (Bethesda)* 20: 260-270, 2005.

Sacchetti, M, Olsen, D.B., Saltin, B., van Hall, G. Heterogeneity in limb fatty acid kinetics in Type 2 diabetes. *Diabetologia*, 48: 938-945, 2005.

Shearer J, Wilson RJ, Battram DS, Richter EA, Robinson DL, Bakovic M and Graham TE. Increases in glycogenin and glycogenin mRNA accompany glycogen resynthesis in human skeletal muscle. *Am J Physiol* 289: E508-E514, 2005.

Shearer J, Graham TE, Battram DS, Robinson DL, Richter EA, Wilson RJ and Bakovic M. Glycogenin activity and mRNA expression in response to volitional exhaustion in human skeletal muscle. *J Appl Physiol* 99: 957-962, 2005.

Scheede-Bergdahl C., M. Penkowa, J. Hidalgo, D.B. Olsen, P. Schjerling, T. Ploug, R. Boushel, and F. Dela. Metallothionein-mediated antioxidant defense system and its response to exercise training are impaired in human type 2 diabetes. *Diabetes* 54:3089-94, 2005.

Strom CC, Aplin M, Ploug T, Christoffersen TE, Langfort J, Viese M, Galbo H, Haunso S, & Sheikh SP. Expression profiling reveals differences in metabolic gene expression between exercise-induced cardiac effects and maladaptive cardiac hypertrophy. *FEBS J* 272, 2684-2695, 2005.

Wojtaszewski JF, Birk JB, Frosig C, Holten M, Pilegaard H, & Dela F. 5'AMP activated protein kinase expression in human skeletal muscle: effects of strength training and type 2 diabetes. *J Physiol* 564, 563-573, 2005.

Zeibig J, Karlic H, Lohninger A, Damsgaard R, Smekal G. Do blood cells mimic gene expression profile alterations known to occur in muscular adaptation to endurance training? *Eur J Appl Physiol* 95(1):96-104, 2005.

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

Ashina M, Jorgensen M, Stallknecht B, Mork H, Bendtsen L, Pedersen JF, Olesen J, & Jensen R. No release of interstitial glutamate in an experimental human model of muscle pain. *Eur J Pain* 9, 337-343, 2005.

Haugaard SB, Andersen O, Dela F, Holst JJ, Storgaard H, Fenger M, Iversen J, & Madsbad S. Defective glucose and lipid metabolism in human immunodeficiency virus-infected patients with lipodystrophy involve liver, muscle tissue and pancreatic beta-cells. *Eur J Endocrinol* 152, 103-112, 2005.

Haugaard SB, Andersen O, Pedersen SB, Dela F, Richelsen B, Nielsen JO, Madsbad S, & Iversen J. Depleted skeletal muscle mitochondrial DNA, hyperlactatemia, and decreased oxidative capacity in HIV-infected patients on highly active antiretroviral therapy. *J Med Virol* 77, 29-38, 2005.

Iqbal SI, Morch LS, Rosenzweig M, & Dela F. The outcome of bone mineral density measurements on patients referred from general practice. *J Clin Densitom* 8, 178-182, 2005.

Trautner, S., O. Amtorp, S. Boesgaard, C.B. Andersen, H. Galbo, S. Haunsoe and M. Sheykhzade: Ca^{2+} -sensitisation and force production by noradrenaline in femoral conductance and resistance arteries from rats with postinfarction congestive heart failure. *Vascul Pharmacol.* In press, 2005.

Research area 2.

Papers in accordance with the CMRC research strategy

Kristensen M, Albertsen J, Rentsch M & Juel C. Lactate and force production in skeletal muscle. *J Physiol* 562: 521-526, 2005.

Nordsborg N, Goodmann C, McKenna MJ, Bangsbo J. Dexamethasone up-regulates skeletal muscle maximal Na^+ , K^+ pump activity by muscle group specific mechanisms in humans. *J Physiol* 567: 583-9, 2005.

Nordsborg N, Thomassen M, Lundby C, Pilegaard H, Bangsbo J. Contraction-induced increases in Na^+ , K^+ -ATPase mRNA levels in human skeletal muscle are not amplified by activation of additional muscle mass. *Am J Physiol* 289(1): R84-91, 2005.

Street D, Nielsen JJ, Bangsbo J, and Juel C. Metabolic alkalosis reduces exercise-induced acidosis and potassium accumulation in human skeletal muscle interstitium. *J Physiol* 566: 481-486, 2005

Østergaard T, Ek J, Hamid Y, Saltin B, Pedersen OB, Hansen T, Schmitz O. Influence of the PPAR- γ 2 Pr12A1a and ACE I/D polymorphisms on insulin sensitivity and training effects in healthy offspring of type 2 diabetic subjects. *Horm Metab Res* 2005; 37: 99-105.

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

Krustrup P., Mohr, M., Ellingsgaard H., and J. Bangsbo. Physical demands of elite female soccer games: Importance of training status. *Med Sci Sports Exerc* 37(7): 1242-1248, 2005.

Mohr, M., Krustrup, P. and Bangsbo, J. Fatigue in soccer – a brief review. *J. Sports Sci.*, 23(6):593-599, 2005.

Research area 3.

Doctor of medical sciences theses (DMSc)

Adam Steensberg: Interleukin-6 in exercise. University of Copenhagen. 20. maj 2005.

PhD-theses

Christian P. Fischer: Interleukin-6 as a hormone. Role in exercise and insulin-resistance. University of Copenhagen. December 2, 2005

Charlotte Keller: Metabolic regulation of the IL-6 response to exercise. University of Copenhagen. November 11, 2005

Sisse Ostrowski: The soluble urokinase receptor in inflammation – with focus on HIV-infection and malaria. University of Copenhagen. March 2005.

Papers in accordance with the CMRC research strategy

Akerstrom T, Steensberg A, Keller P, Keller C, Penkowa M, Pedersen BK. Exercise induces interleukin-8 expression in human skeletal muscle. *J Physiol* 563: 507-516, 2005.

Brunsgaard, H. Physical activity and modulation of systemic low-level inflammation. *J Leukoc. Biol.* 78(4):819-35. 2005.

Febbraio MA, Pedersen BK. Contraction-induced myokine production and release: evidence that the skeletal muscle is an endocrine organ? *Exerc Sport Sci Rev* 33(3): 114-119, 2005.

Fischer CP, Perstrup LB, Berntsen A, Eskildsen P, Pedersen BK. Elevated plasma interleukin –18 is an inflammatory marker of insulin-resistance in type 2 diabetic and non-diabetic humans. *Clin Immunol* 117(2): 152-160, 2005.

Hansen AK, Fischer C, Plomgaard P, Andersen JL, Saltin B, Pedersen BK. Skeletal muscle adaptation: Training twice every second day versus training once daily. *J Appl Physiol* 98: 93-99, 2005

Hiscock N, Fischer CP, Sacchetti M, van Hall G, Febbraio MA, Pedersen BK. Recombinant human interleukin-6 infusion during low intensity exercise does not enhance whole body lipolysis or fat oxidation in humans. *Am J Physiol* 289(1): E-2-7, 2005.

Hoffman-Goetz L, Pedersen BK. Exercise and the immune system. In: *Exercise-physiological aspects. Advanced Exercise Physiology*. Tipton CM (ed). Indianapolis: American College of Sports Medicine: 482-500, 2005.

Keller P, Keller C, Steensberg A, Robinson LE, Pedersen BK. Leptin gene expression and systemic levels in healthy men: Effect of exercise, carbohydrate, interleukin-6, and epinephrine. *J Appl Physiol* 98(5):1805-1812, 2005.

Keller P, Penkowa M, Keller C, Steensberg A, Fischer CP, Giralt M, Hidalgo J, Pedersen BK. Interleukin-6 receptor expression in contracting human skeletal muscle: regulating role of IL-6. *FASEB J* 19(9): 1181-1183, 2005

Pedersen BK. Natural immunity – effect of exercise. In: Bertók L, Chow DA (eds). *Neuroimmune Biology*; vol. 5: 263-288, 2005.

Pedersen BK, Febbraio M. Muscle-derived interleukin-6 – a possible link between skeletal muscle, adipose tissue, liver and brain. *Brain, Behav Immun* 19: 371-376, 2005.

Penkowa M, Keller P, Keller C, Hidalgo J, Giralt M, Pedersen BK. Exercise-induced metallothionein expression in human skeletal muscle fibres. *Exp Physiol* 90(4):477-486, 2005.

Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. *J Appl Physiol* 98(4): 1154-1162, 2005.

Petersen EW, Carey AL, Sachetti M, Steinberg GR, Macaulay SL, Febbraio MA, Pedersen BK. M. Acute IL-6 treatment increases fatty acid turnover in elderly humans in vivo and in tissue culture in vitro. *Am J Physiol* 288(1): E155-162, 2005.

Plomgaard P, Bouzakri K, Krogh-Madsen R, Zierath JR, Pedersen BK. TNF- α induces skeletal muscle insulin resistance in healthy human subjects via inhibition of AS160 phosphorylation. *Diabetes* 54(10): 2939-2945, 2005.

Plomgaard P, Keller P, Keller C, Pedersen BK. TNF- α , but not IL-6, stimulates plasminogen activator inhibitor 1 (PAI-1) expression in human subcutaneous adipose tissue. *J Appl Physiol* 98: 2019-2023, 2005.

Plomgaard P, Penkowa M, Pedersen BK. Fiber type specific expression of TNF-alpha, IL-6 and IL-18 in human skeletal muscles. *Exerc Immunol Rev* 11:53-63, 2005.

Watt MJ, Carey A, Wolsk-Petersen E, Pedersen BK, Febbraio MA. Hormone sensitive lipase is reduced in the adipose tissue of patients with type 2 diabetes mellitus: influence of Il-6 infusion. *Diabetologia* 48(1): 105-112, 2005.

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

Johansen JS, Krabbe KS, Møller K, Pedersen BK. Circulating YKL-40 levels during human endotoxemia. *Clin Exp Immunol* 140: 343-348, 2005.

Krabbe KS, Reichenberg A, Yirmiya R, Smed A, Pedersen BK, Bruunsgaard H. Low dose endotoxemia and human neuropsychological functions. *Brain, Behav, Immunol* 19 (5): 453-460, 2005.

Macisaac RJ, Tsalamandris C, Panagiotopoulos S, Smith TJ, McNeill KJ, Jerums G, Bai X, Miao D, Li J, Goltzman D, Karaplis AC, Nemeth E, Rivera S, Gabayan V, Keller C, Taudorf S, Pedersen BK, Ganz T. Type 2 diabetes: absence of proteinuria does not preclude loss of renal function: nonalbuminuric renal insufficiency in type 2 diabetes. *J Am Soc Nephrol* 16(2): 284-290, 2005.

Moller K, Tofteng F, Qvist T, Sahl C, Sonderkaer S, Pedersen BK. Cerebral output of cytokines in patients with pneumococcal meningitis. *Crit Care Med* 33(5): 979-983, 2005.

Ostrowski SR, Katzenstein TL, Thim PT, Pedersen BK, Gerstoft J, Ullum H. Low-level viremia and proviral DNA impede immune reconstitution in HIV-1-infected patients receiving highly active antiretroviral therapy. *J Infect Dis* 191: 348-357, 2005

Ostrowski SR, Piironen T, Hoyer-Hansen G, Gerstoft J, Pedersen BK, Ullum H. High plasma levels of intact and cleaved soluble urokinase receptor reflect immune activation and are independent predictors of mortality in HIV-1-infected patients. *J Acquir Immune Defic Syndr* 39(1): 23-31, 2005.

Ostrowski SR, Piironen T, Hoyer-Hansen G, Gerstoft J, Pedersen BK, Ullum H. Reduced release of intact and cleaved urokinase receptor in stimulated whole-blood cultures from human immunodeficiency virus-1-infected patients. *Scand J Immunol* 61: 347-356, 2005.

Ostrowski SR, Plomgaard PS, Fischer CP, Steensberg AS, Møller K, Høyer-Hansen G, Pedersen BK, Ullum H. Interleukin-6 infusion during human endotoxemia inhibits in vitro release of the urokinase receptor from peripheral blood mononuclear cells. *Scand J Immunol* 61: 197-206, 2005.

Ostrowski SR, Ullum H, Goka BQ, Høyer-Hansen G, Obeng-Adjei G, Pedersen BK, Akanmori BD, Kurtzhals JAL. Plasma concentrations of soluble urokinase-type plasminogen activator receptor are increased in patients with malaria and are associated with a poor clinical or a fatal outcome. *J Infect Dis* 191: 1331-1341, 2005.

Ostrowski SR, Ullum H, Pedersen BK, Gerstoft J, Katzenstein TL. 2B4 expression on natural killer cells increases in HIV-1 infected patients followed prospectively during highly active antiretroviral therapy. *Clin Exp Immunol* 141(3):526-533, 2005.

Pedersen BK. [Children and exercise]. Copenhagen: Nyt Nordisk Forlag Arnold Busck; 2005.

Pedersen BK. Nutrition and the immune system. In: Human nutrition from molecular biology to sociology, 2nd edition. Astrup A, Garby L, Stender S. (eds). Copenhagen: Munksgaards forlag, 2005: 400-404.

Richelsen B, Andersen NL, Flint A, Hermansen K, Osler M, Pedersen BK. Scientific evaluation of the "upturned" diet pyramid. *Ugeskr Laeger* 167(8): 927-931, 2005.

Research area 4.

Doctor of medical sciences theses (DMSc)

Mads Dalsgaard: Fuelling cerebral activity in exercising man. Københavns Univeristet. 2.12.05

-

Berend E Westerhof: Blood pressure analysis on time scales from seconds to days. University of Amsterdam 13.12.05.

Papers in accordance with the CMRC research strategy

Blomstrand E, K Møller, NH Secher and L Nybo. Effect of carbohydrate ingestion on brain exchange of amino acids during sustained exercise in human subjects. *Acta Physiol Scand* 185: 203-209, 2005.

- Fisher JP, Sander M, MacDonald I, White MJ. Decreased muscle sympathetic nerve activity does not explain increased vascular conductance during contralateral isometric exercise in humans. *Exp Physiol* 90(3):377-382, 2005.
- Calbet, J.A.L., Holmberg, H.-C., Rosdahl, H., van Hall, G., Jensen-Urstad, M., Saltin, B. Why do the arms extract less oxygen than the legs during exercise? *Amer J Physiol* 289:R1448-58, 2005.
- Krantz T, J Warberg and NH Secher. Venous oxygen saturation during normovolaemic haemodilution in the pig. *Acta Anaesthesiol Scand* 49: 1149-1156, 2005.
- van Lieshout JJ, MPM Harms, F Pott, M Jenstrup and NH Secher. Stroke volume and central vascular pressures during tilt in humans. *Acta Anaesthesiol Scand* 49: 1287-1292, 2005.
- Lundby C, Nielsen TK, Dela F, & Damsgaard R. The influence of intermittent altitude exposure to 4100 m on exercise capacity and blood variables. *Scand J Med Sci Sports* 15, 182-187, 2005.
- Mortensen SP, EA Dawson, CC Yoshiga, MK Dalsgaard, R Damsgaard, NH Secher and J Gonzalez-Alonso. Limitations to systemic and locomotor limb muscle oxygen delivery and uptake during maximal exercise in humans. *J Physiol* 566: 273-285, 2005.
- Nielsen HB, NH Secher and P Ott. Maintained cerebral and skeletal muscle oxygenation during maximal exercise in patients with liver failure. *J Hepatol* 43: 266-271, 2005.
- Nowak M, S Holm, F Biering-Sørensen, NH Secher and L Friberg. "Central command" and insular activation during attempted foot lifting in paraplegic humans. *Hum Brain Mapp* 25: 259-265, 2005.
- Nybo L, MK Dalsgaard, A Steensberg, K Møller and NH Secher. Cerebral ammonia uptake and accumulation during prolonged exercise in humans. *J Physiol* 563: 285-290, 2005.
- Ogoh S, MK Dalsgaard, CC Yoshiga, EA Dawson, DM Keller, PB Raven and NH Secher. Dynamic cerebral auto regulation during exhaustive exercise in humans. *Am J Physiol* 288: H1461- H1467, 2005.
- Ogoh S, PJ Fadel, R Zhang, C Selmer, Ø Jans, NH Secher and PB Raven. Middle cerebral artery flow velocity and pulse pressure during dynamic exercise in humans. *Am J Physiol* 288: H1526-H1531, 2005.
- Ogoh S, JP Fisher, EA Dawson, MJ White, NH Secher and PB Raven. Autonomic nervous system influence on arterial baroreflex control of heart rate during exercise in humans. *J Physiol* 566: 599-611, 2005.
- Schou M, MK Dalsgaard, O Clemmesen, EA Dawson, CC Yoshiga, HB Nielsen, F Gustafsson, PR Hildebrandt, and NH Secher. The kidneys extract BNP and NT-proBNP in healthy young males. *J Appl Physiol* 99: 1676-1680, 2005.
- Secher NH and B Quistorff. Brain glucose and lactate uptake in humans during exhaustive exercise (Perspective). *J Physiol* 568: 3, 2005.
- Secher NH and JJ Van Lieshout. Normovolaemia defined by central blood volume and venous oxygen saturation. *Clin Exp Pharm Physiol* 32: 901-10, 2005.
- Shibasaki M, NH Secher, JM Johnson and CG Crandall. Central command and the cutaneous vascular response to isometric exercise in heated humans. *J Physiol* 565: 667-673, 2005.
- Stirling JR, Zakyntinaki MS, Saltin B. A model of oxygen uptake kinetics in response to exercise: including a means of calculating oxygen demand/deficit/debt. *Bull Math Biol*; 67(5): 989-1015, 2005.

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

Nielsen HB, C Thomsen, X Chen, CB Andersen, BG Toft, L Søndergaard, S Haunsø and JH Svendsen. Arrhythmogenic right ventricular cardiomyopathy: a presentation of thirty consecutive patients. *Heart Drug* 5: 146-152, 2005.

Research area 5.

Papers in accordance with the CMRC strategy

Bogdanovich S, Perkins KJ, Krag TO, Whittemore LA, Khurana TS. Myostatin propeptide-mediated amelioration of dystrophic pathophysiology. *FASEB J* 2005; 19(6): 543-549.

Hanish F, Hellsten Y, Zierz S. Ecto- and cytosolic 5'-nucleotidases in normal and AMP deaminase deficient human skeletal muscle. *Biological Chemistry* (in press).

Mittendorfer B, Andersen JL, Plomgaard P, Saltin B, Babraj JA, Smith K, Rennie MJ. Protein synthesis rates in human muscles: neither anatomical location nor fibre-type composition are major determinants. *J Physiol* 2005; 563: 203-11.

Olsen DB, Ørngreen MC, Vissing J. Aerobic training improves exercise performance in facioscapulohumeral muscular dystrophy. *Neurology* 2005; 64: 1064-1066.

Schwartz M, Hertz JM, Sveen ML, Vissing J. LGMD2I presenting with a characteristic Duchenne or Becker dystrophy phenotype. *Neurology* 2005; 64: 1635-1637.

Sveen ML, Schwartz M, Vissing J. High prevalence and phenotype-genotype correlation of LGMD21 in Denmark. *Ann Neurol* 2005; in press.

Vissing J, Quistorff B, Haller RG. Effect of fuels on exercise capacity in muscle phosphoglycerate mutase deficiency. *Arch Neurol* 2005; 62: 1440-1443.

Ørngreen MC, Dunø M, Christensen E, Sacchetti M, Schwartz M, Vissing J. Fuel utilization in subjects with carnitine palmitoyltransferase II gene mutations. *Ann Neurol* 2005; 57: 60-66.

Ørngreen, MC, Olsen DB, Vissing J. Aerobic training in patients with myotonic dystrophy type I. *Ann Neurol* 2005; 57: 754-757.

Østergaard E, Wibrand F, Ørngreen MC, Vissing J, Horn N. Impaired energy metabolism and abnormal muscle histology in mut- methylmalonic aciduria. *Neurology* 2005; 65: 931-934.

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

Anthonisen M, Toft R, Rønager J, Vissing J. Patientgrundlag og evaluering af undersøgelser i en neuromuskulær klinik gennem tre år. *Ugeskr Læger* 2005; 167(22): 2405-2408.

Research area 6.

PhD-theses

Jens Bojsen-Møller: Mechanical properties of the human tendon-aponeurosis complex in vivo measured by ultrasonography: Methodological, physiological and functional aspects. University of Copenhagen, 1. september 2005.

Louise Pyndt Diederichsen: Afferent signalling and muscular coordination in normal and painful shoulder, University of Copenhagen, October 7, 2005.

Anne Katrine Blangsted: Significance of sustained low-force contractions on acute and long-term muscle fatigue development, University of Copenhagen, March 10, 2005.

Papers in accordance with the CMRC research strategy

Andersen LL, Aagaard P: Influence of maximal muscle strength and intrinsic muscle contractile properties on contractile rate of force development. *Eur J Appl Physiol*, 26, 1-7, 2005.

Andersen LL, Andersen JL, Magnusson SP, Aagaard P. Neuromuscular adaptations to detraining following resistance training in previously untrained subjects. *Eur J Appl Physiol*, 93, 511-518, 2005.

Andersen LL, Andersen JL, Magnusson SP, Suetta C, Madsen JL, Christensen LR, Aagaard P. Changes in the human muscle force-velocity relationship to resistance training and subsequent detraining. *J Appl Physiol*, 99:87-94, 2005.

Andersen LL, Tofekovic G, Zebis MK, Crameri R, Verlaan, G, Kjaer M, Suetta C Magnusson SP, Aagaard P: The effect of resistance training combined with timed ingestion of protein on muscle fiber size and muscle strength. *Metabolism*, 54:151-6, 2005.

Babraj JA, Cuthbertson DJ, Smith K, Langberg H, Miller B, Krogsgaard MR, Kjaer M, Rennie MJ: Collagen synthesis in human musculoskeletal tissues and skin. *Amer J Physiol*, 289:E864-9, 2005.

Bojsen-Moller J, Magnusson SP, Rasmussen LR, Kjaer M, Aagaard P: Muscle performance during maximal isometric and dynamic contractions is influenced by the stiffness of the tendinous structures. *J Appl Physiol*, 99, 986-994, 2005.

Coker RH, Kjaer M. Glucoregulation during exercise: the role of the neuroendocrine system. *Sports Med*, 35: 575-583, 2005.

Doessing S, Kjaer M. Growth hormone and connective tissue in exercise. *Scand J Medi Sci Sports*, 15: 202-210, 2005.

Hannukainen J, Kalliokoski KK, Nuutila P, Fujimoto T, Kempainen J, Viljanen T, Laaksonen MS, Parkkola R, Knuuti J, Kjaer M. In vivo measurements of glucose uptake in human achilles tendon during different exercise intensities. *Int J Sports Med*, 26: 727-731, 2005. Hansen M, Morthorst R, Larsson B, Dall R, Flyvbjerg A, Rasmussen MH, Orskov H, Kjaer M, Lange KH: No effect of growth hormone administration on substrate oxidation during exercise. *J Physiol*, 15; 567(Pt 3):1035-1045, 2005.

Hansen M, Morthorst R, Larsson B, Flyvbjerg A, Rasmussen MH, Orskov H, Astrup A, Kjaer M, Lange KH: Effects of two weeks GH-administration on 24 hours indirect calorimetry in young, healthy, lean men. *Amer J Physiol*, 289: E1030-E1038, 2005.

Hansen P, Bojsen-Moller, Aagaard P, Magnusson SP: Mechanical properties of the human patellar tendon, in vivo. *Clin Biomechanics*, 21: 54-58, 2005.

Haraldsson BT, Aagaard P, Krogsgaard M, Kjaer M, Magnusson SP: Region specific mechanical properties of the human patella tendon. *J Appl Physiol*, 98, 1006-1012, 2005.

Harridge S, Saltin B. Neuromuscular system and ageing. In: *Physical functions in elderly*. London 2005 (under publication).

Holm L, Esmarck B, Suetta C, Matsumoto K, Doi T, Mizuno M, Miller BF, Kjaer M: Postexercise nutrient intake enhances leg protein balance in early postmenopausal women. *J Gerontol Med Sci*, 60A (9): 1212-1218, 2005.

Kadi F, Charifi N, Denis C, Lexell J, Andersen JL, Schjerling P, Olsen SA, Kjaer M. The behaviour of satellite cells in response to exercise: what have we learned from human studies? *Pflugers Archiv* 451: 319-327, 2005.

Kalliokoski KK, Langberg H, Ryberg AK, Scheede-Bergdahl C, Doessing S, Kjaer A, Boushel R, Kjaer M: The effect of dynamic knee-extension exercise on patellar tendon and quadriceps femoris muscle glucose uptake in humans studied by positron emission tomography. *J Appl Physiol*, 99:1189-92, 2005.

Kjaer M, Langberg H, Miller BF, Boushel R, Crameri R, Koskinen S, Heinemeier K, Olesen JL, Dossing S, Hansen M, Pedersen SG, Rennie MJ, Magnusson P: Metabolic activity and collagen turnover in human tendon in response to physical activity. *J Musculoskeletal Neuronal Interaction* 1: 41-52, 2005.

Kongsgaard M, Aagaard P, Kjaer M, Magnusson SP: Structural Achilles tendon properties in athletes subjected to different exercise modes and in Achilles tendon rupture patients. *J Appl Physiol*, 99:1965-71, 2005.

Kyrolainen, H., Avela, J., McBride, J.M., Koskinen, S., Andersen, J.L., Sipila, S., Takala, T.E. & Komi, P.V. Effects of power training on muscle structure and neuromuscular performance. *Scand. J. Med. Sci. Sports*. 15, 58-64, 2005.

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*, 15:567:1021-33, 2005.

Rosendal L, Søgaard K, Kjaer M, Sjøgaard G, Langberg H, Kristiansen J. Increase in interstitial interleukin-6 of human skeletal muscle with repetitive low-force exercise. *J Appl Physiol*, 98: 477-481, 2005.

Rosendal L, Kristiansen J, Gerdle B, Søgaard K, Peolsson M, Kjaer M, Sørensen J, Larsson B: Increased levels of interstitial potassium but normal levels of muscle IL-6 and LDH in patients with trapezius myalgia. *Pain* 119: 201-209, 2005.

Rudroff T, Poston B, Shin I-S, Bojsen-Møller J, Enoka RM: Net excitation of the motor unit pool varied with load type during fatiguing contractions. *Muscle & Nerve*, 31(1) 78-87, 2005.

K. Vissing, J.L. Andersen, and P. Schjerling. Are exercise-induced genes induced by exercise? *FASEB J*. 19:94-6, 2005.

Vissing K, Andersen JL, Harridge SD, Sandri C, Hartkopp A, Kjaer M, Schjerling P. Gene expression of myogenic factors and phenotype-specific markers in electrically stimulated muscle of paraplegics. *J Appl Physiol*, 99: 164-172, 2005.

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

Aagaard P. Passive and dynamic joint stabilization in the normal and anterior cruciate ligament-deficient knee (Editorial). *Scand J Med Sci Sports* 15: 137-138, 2005.

Aagaard P, Bangsbo J: The muscular system: design, function and performance relationships. Kapitel 6 i *Advanced Exercise Physiology* (Eds Tipton CM, Terjung RL et al), American College of Sports Medicine; Lippincot, Williams & Wilkins: 144-160, 2005.

Kjær M. The adrenal gland: Fight or flight implications for sports. In: *Endocrinology of Physical Activity and Sports*. Chapter 15. Eds: Kraemer and Rogol, Int.Olymp Committee. Blackwell. pp 194-200, 2005.

Vinther A, Alkjaer T, Kanstrup I, Larsson B, Magnusson SP, Aagaard P: Exercise induced rib stress fractures: Influence of reduced bone mineral density. *Scand J Med Sci Sports* 15:95-9, 2005.

Vinther A, Christiansen E, Kanstrup IL, Alkjær T, Larsson B, Magnusson SP, Ekdahl C, Aagaard P. Exercise-induced rib stress fractures: Potential risk factors related to thoracic muscle co-contraction and movement pattern: *Scand J Med Sci Sports* 15, 95-99, 2005.

Invited lectures

Research area 1.

Henrik Galbo: "The Influence of exercise on cardiovascular risk factors, morbidity and mortality in diabetes" at The First Int. Meeting on Physical Activity and Diabetes Mellitus, Catania 01.07.05.

Henrik Galbo. "The influence of exercise on cardiovascular risk factors, morbidity and mortality in diabetes" at "The 3rd International Congress of Sports Medicine", Thessaloniki, 09.12.2005.

Nils Halberg: The effect of intermittent fasting on insulin sensitivity - a mechanism for exercise? 60th Annual Meeting of the Japanese Society of Physical Activity and Sports Medicine. Kurashiki, Japan. 22 September 2005.

Jørn Wulff Helge:

"Arm and leg metabolism after prolonged low intensity training". Dansk Idrætsmedicinsk årsmøde, Århus. Januar.

"Training and insulin resistance". 19th. International Puijo Symposium, Kuopio, Finland. 30 juni 2005.

"Metabolism of ultra endurance exercise". New Zealand Sports Medicine and Science Congress. Queenstown, 3 November, 2005.

"Metabolic Fitness and Insulin resistance". New Zealand Sports Medicine and Science Congress. Queenstown, New Zealand. 5 November, 2005.

Henriette Pilegaard:

"Adaptive gene response in human arm and leg skeletal muscle". Idrætsmedicinsk Årskongres, Aarhus, February, 2005.

"Role of PGC-1 α in muscle training response". International Union of Physiological Sciences, San Diego, April 2005.

Erik A. Richter:

"The Edward F. Adolph Distinguished Lecture" at the International Physiological Society's and American Physiological Society's meeting in San Diego, 3. april 2005 and received the accompanying Award.

International Second Messenger Symposium, Dundee, Scotland. "Physiology of AMPK in muscle related to exercise and diabetes".

International XVIII Puijo Symposium, Kuopio, Finland. "Molecular mechanisms underlying glucose transport in exercising muscle".

Bengt Saltin:

WHO/IOC Conference: "Sports for all in the combat of type 2 diabetes", Rom, Italy 2005.

Lunds Universitet: "Fysisk aktivitet ved svær overvægt", Sverige, april 2005.

Asian Conference on Exercise and Health: "Role of exercise in prevention and treatment of type 2 diabetes", Tokyo, Japan, May 2005.

Research area 2.

Jens Bangsbo:

Physiological Society Special Symposium: The metabolism of intermittent exercise: "Limitations in repeated intense exercise", 4th Sept. 2005, Loughborough University.

Physiological Society Special Symposium: The metabolism of intermittent exercise: "High intensity exercise performance", 5th Sept. 2005, Loughborough University.

Peter Krstrup: Gæsteforelæsning på Facultat de Ciències de l'Activitat Física i l'Esport, Valencia, Spanien.

"Metabolic demands during intense intermittent exercise, effects of aerobic and anaerobic training".

Research area 3.

Bente Klarlund Pedersen:

Lifestyle Medicine Symposium/Healthy People 2005 conference: "Exercise, cytokines and metabolism", March 2005, Loma Linda, California, USA.

35th FASEB meeting International Congress on Physiological Sciences: "Muscle as an endocrine organ – focus on muscle-derived IL-6", April 2005, San Diego, California, USA.

American Diabetes Association's 65th Scientific Sessions: "Is IL-6 a bad actor?", June 2005, San Diego, California, USA.

Canadian Federation of Biological Sciences, 48th annual meeting of CFBS 2005 (key-note speaker): "Muscle-derived IL-6 and its role on metabolism", June 2005, Guelph, Canada.

The International 18th Puijo Symposium: Physical exercise, inflammation and immunology", June 2005, Kuopio, Finland.

10th Annual Congress of the European College of Sport Science: "Exercise, cytokines and oxidative stress", July 2005, Belgrade, Serbia & Monte Negro.

10th Annual Congress of the European College of Sport Science: "Rather Fat and Fit than Slim and Sedentary?", July 2005, Belgrade, Serbia & Monte Negro.

7th European Congress of Endocrinology: "Cytokines, Fat and Muscle", September 2005, Göteborg, Sweden.

7th International Society of Exercise and Immunology Symposium: "IL-6 and Exercise—an update", September 2005, Monaco.

Christian P. Fischer: ECSS: "The role of antioxidants in the regulation of exercise-induced cytokine production and metabolism", Belgrade, Serbia, 14 July 2005.

Helle Bruunsgaard: French National Committee for Physical Activities and Sports. Symposium on Health, Sports and Innovations: "Aging, exercise and immunology", Bruxelles, May 2005.

Research area 4.

Ylva Hellsten:

"Reactive oxygen species and gene expression in skeletal muscle", The Annual Meeting of the French Physiological Society, 28. June 2005.

"Antioxidants and gene expression in skeletal muscle", European Congress Sports Science, Belgrade, 16. July 2005.

Henning Bay Nielsen: "Cardiovascular Screening", World Rowing Forum, Istanbul, Turkey 03.11.05.

Henriette Pilegaard: "Physical exercise and gene expression", The International 18th Puijo Symposium: "Physical activity in Conjunction with Pharmacological Therapy for Chronic Vascular Diseases", Kuopio, Finland, June 2005.

Bengt Saltin: The opening of ASPIRE: "The search for and fostering of the young talent", Doha, Qatar, November 2005.

Niels Secher:

"The arms and legs in competition for cardiac output?", Am Coll Sports Med, Nashville, 02.06.05.

"Anæstesiologisk og intensiv medicin forskning i globalt perspektiv. Problemer og muligheder", Dansk Selskab for Anæstesiologi og Intensiv Medicins årsmøde, 04.11.05.

"What is normovolaemia?" Dansk Kirurgisk Selskabs årsmøde, 03.11.05.

"Train the Brain". World Rowing Forum, Istanbul, Turkey 03.11.05.

Frans Swiatek: "CVK med ultralyd", Dansk Selskab for Anæstesiologi og Intensiv Medicins Årsmøde 03.11.05.

Research area 5.

John Vissing:

"Aerobic training" ved workshop om mitochondrial disorders", 17. Kongress des wissenschaftlichen beirates der Deutschen Gesellschaft für Muskelkranke", Dresden, Tyskland.

"Mitochondrial disease in Neurology" ved Dansk Neurologisk Selskabs årsmøde i Munkebjerg, Vejle.

"Limb girdle muscular dystrophy". NORFA kursus i muskelsygdomme. Gässlingen, Sweden.

Fire inviterede foredrag som led i visiting professorship ved Neuromuscular Centre, University

hospital Nijmegen, Holland.

Research area 6.

Jens Boysen-Møller. "Mechanical and structural properties of the human aponeurosis-tendon structure measured in vivo", 10th Annual Congress of the European College of Sport Science, Belgrade, Serbia, 2005.

Michael Kjær:

"Preventing tendinopathy". Symposium on injury prevention. 1st World Congress on Sports Injury Prevention. Oslo, Norway, June 2005.

"Extracellular matrix adaptation of tendon and skeletal muscle to exercise". The Anatomical Society Congress, Cardiff University, Wales, July 2005.

"The first 10 years - historical lecture", European College of Sports Science 10th Annual Congress, Belgrade, Serbia-Montenegro, July 2005.

"Skeletal muscle in an ageing perspective", Post-graduate Course, NORFA, Nässlingen, Sweden, August 2005.

"Funktionelle Anpassungen bei Älteren", 39. Kongress der Deutschen Gesellschaft für Sportsmedizin und Prävention, Hamburg, Tyskland, Sept. 2005.

"Adaptations in connective tissue of tendon and skeletal muscle with physical activity: Implications for elderly", Int.workshop ("SPARK") on Elderly and Frailty, Unilever, Amsterdam, Nov 2005.

"Tendinopathy – current concepts of causal mechanisms and treatment". Int.conference on Neuromuscular Interaction, Jyväskylä University, Jyväskylä, Finland, Dec. 2005.

Henning Langberg:

"Senevævet's adaptation til belastning". Privatpraktiserende Fysioterapeuters Gruppe - årsmøde, Geilo, Norge, januar 2005.

"Fodens biomekanik". Privatpraktiserende Fysioterapeuters Gruppe - årsmøde, Geilo, Norway, January, 2005.

"Prevention of sports injuries". American College of Sports Medicine, Nashville, USA, June, 2005.

"Prevention of Sports Injuries" European College of Sports Medicine, Belgrade, Slovenia, July, 2005.

"Tendon responses to loading and overloading – implications for injury and treatment" European College of Sports Medicine, Belgrade, Slovenia, July, 2005.

"Prevention of Injuries in Sports". Int. Federation for Sports Physiotherapy-congress, Oslo, Norge, June, 2005.

"Biomechanics of the lower leg". 5th Jornadas de Fisioterapia no Desporto, Rio Maior, Portugal, October, 2005.

"New research on tendons and tendon problems". 5th Jornadas de Fisioterapia no Desporto, Rio Maior, Portugal, October, 2005.

"Treatment of Achilles tendon and Patella problems". 5th Jornadas de Fisioterapia no Desporto, Rio Maior, Portugal, October, 2005.

"Tendons injuries in sports", Høstkongress, Norsk Idrætsmedicinsk Selskab, Bergen, Norway, November, 2005.

"Biomechanics of the lower extremity", Høstkongress, Norsk Idrætsmedicinsk Selskab, Bergen, Norway, November, 2005.

"Use of insoles in Sports", Høstkongress, Norsk Idrætsmedicinsk Forening, Bergen, Norway, November, 2005.

"Adaptation/overuse and healing of tendons" Anual meeting, Sportsfizio, Bern, Schweiz, November, 2005.

Peter Magnusson:

"A biomechanical evaluation of stretching the muscle-tendon unit." Symposium on stretching: Annual Swedish Sports Medicine Meeting, Karlstad, Sweden, April, 2005.

"Musculoskeletal stretching – a panacea". Symposium on injury prevention. 1st World Congress on Sports Injury Prevention. Oslo, Norway, June 2005.

Bengt Saltin. WHO/FN World Aging and Generations Congress: "Aging skeletal muscle and function", St. Gallen, Schweiz, September 2005.

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

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

Carsten Juel. Member of Editorial Board at European Journal of Applied Physiology.

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

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

Bente Klarlund Pedersen. Member of editorial board at European Journal of Applied Physiology, Exercise Immunology Reviews, Journal of Applied Physiology, Pflügers Archiv – European Journal of Physiology, Experimental Physiology and Exercise Immunology Reviews.

Erik A. Richter. Associate Editor at Journal of Applied Physiology.

Bengt Saltin. Member of editorial board Journal of Applied Physiology.

Niels H. Secher. Editor European J Appl Physiol og Exp Physiol, Editorial board J Appl Physiol, J Sports Sci og Scand J Med Sci Sports Exerc.

Jørgen Wojtaszewski. Associate Editor at Journal of Applied Physiology.

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

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

Bente Kiens. Member of "The Academic Advisory Board" for the IOC (International Olympic Committee) course on Sports Nutrition.

John Vissing. Member of Scientific Committee for European Neuromuscular Centre.

Jens Bangsbo. Evaluated PhD-thesis: Nikolai Nordsborg: "Effect of exercise on interstitial K⁺, fatigue development and Na⁺, K⁺ pump mRNA expression in human muscle", University of Copenhagen. .

Jens Bangsbo. Evaluated PhD-thesis: Sebastian B. Jørgensen: "The role of the AMPK in regulation of glucose metabolism and expression of metabolic genes and proteins in skeletal muscle", University of Copenhagen.

Flemming Dela. Evaluated PhD-thesis: Jens Bojsen-Møller, cand.scient. "Mechanical properties of the human tendon-aponeurosis complex in vivo measured by ultrasonography: Methodological, physiological and functional aspects", University of Copenhagen (2005).

Flemming Dela. Evaluated PhD-thesis: Steen Schytte Olsen, cand.scient. "Creatinine supplementation augments the increase in satellite cells and myonuclei in skeletal muscle of young men following strength training", University of Copenhagen (2005).

Flemming Dela. Evaluated PhD-thesis: Lei Zhang, Bsc."Insulin-Mediated Capillary Recruitment: Regulatory and Anatomical Aspects", University of Tasmania, Australien (2005).

Jørn Wulff Helge. Evaluated PhD-thesis: "Metabolic and hormonal responses to altered carbohydrate availability and its effects on fatigue development" by Amanda Claassen. University of Cape Town, South Africa (2005).

Jørn Wulff Helge. Evaluated PhD-thesis: "Obesity, physical exercise and growth in children population from Gran Canaria: Longitudinal study". Ignacio Ara Royo. University of Las Palmas, Gran Canaria, Spain (2005).

Ylva Hellsten. Evaluated PhD-thesis: Thomas Gustaffson, "Exercise and angiogenic growth factors in human skeletal muscle", Karolinska Institutet, Stockholm.

Michael Kjær. Evaluated doctoral thesis: Helene Nørrelund, "The metabolic role of growth hormone in humans with particular reference to fasting", University of Aarhus.

Michael Kjær. Evaluated doctoral thesis: Henning Bundgaard, "Potassium regulation in heart and skeletal muscles", University of Copenhagen.

Michael Kjær. Evaluated PhD-thesis: Torben Østergaard, "Aspects of insulin resistance in physical fitness in first degree relatives of patients with type 2 diabetes. The effect of exercise training". University of Aarhus.

Michael Kjær. Evaluated PhD-thesis: German Rodriguez, "Growth and bone mass. Effect of physical activity – a longitudinal study", University of Las Palmas, Gran Canaria, Spain,

Michael Kjær. Evaluated PhD-thesis: Ling Guo, "Animal models for muscular dystrophy, mechanism of disease and potential therapy",

Peter Magnusson. Evaluated doctoral thesis: Hans Christer Holmberg, "Physiology of cross country skiing – with special emphasis on the role of the upper body", Karolinska Institutet, Stockholm.

Peter Magnusson. Evaluated PhD-thesis: Marko Laaksonen, "The acute effects of exercise on skeletal muscle blood flow. Positron emission tomography studies in healthy subjects", Turku University, Finland.

Bente Klarlund Pedersen. Evaluated doctoral thesis: Ole E. Sørensen, "The human cathelicidin hCAP-18", University of Copenhagen.

Bente Klarlund Pedersen. Evaluated PhD-thesis: Helena Domingues, "The role of tumor necrosis factor alpha on insulin resistance and vascular dysfunction", University of Copenhagen.

Bente Klarlund Pedersen. Evaluated PhD-thesis: Beate Boruta Malmquist, "Flow-mediated dilation. The link between Chlamydia pneumoniae antibodies and ischemic heart disease. The effect of clarithromycin on endothelial function in men with acute coronary syndrome", University of Copenhagen.

Bente Klarlund Pedersen. Chairman of board of evaluation for senior group leaders (professor) and junior group leaders (associate professor) at BRIC.

Erik A. Richter. Evaluated doctoral thesis: Michael Gaster, "Fibre type dependent expression of glucose transporters in human skeletal muscles. An immunohistochemical approach". University of Southern Denmark.

Bengt Saltin. Evaluated PhD-thesis: Stig Eiberg Hansen, "Physical Fitness, Physical Activity and Cardiovascular Disease. The Copenhagen School Child Intervention Study". University of Copenhagen October 2005.

Bengt Saltin. Evaluated doctoral thesis: Ingrid Wernstedt, "Metabolic Effects of Interleukin-6", Sahlgrenska Academy, Göteborg University, December 2005.

Niels H. Secher: Evaluated doctoral thesis: H.C. Holmberg, Physiology of Cross-Country Skiing with special emphasis on the role of the upper body. Karolinska Institutet, Stockholm, 16.09.05.

Niels H. Secher. Evaluated PhD-thesis: Jesper Filtenborg Tvedskov, "A human experimental migraine model using glyceryltrinitrate for evaluating prophylactic treatment", 13.05.05, University Hospital Glostrup.

Niels H. Secher. Evaluated applicants for a professorship in perioperative pathophysiology, University of Copenhagen.

Symposia and PhD courses arranged by CMRC

Research area 4.

Symposium for Bengt Saltin (70 years), The August Krogh Institute, 28.05.05.

PhD course: Integrative human cardiovascular control, Rigshospitalet 22.-27.05.05.

Seminars

02.03.05 The August Krogh Institute. "Glucose transport in skeletal muscle".

18.04.05 The August Krogh Institute. "Molecular Biology".

03.06.05 The August Krogh Institute. CMRC Youngsters arrangement. "Tips on a successful oral presentation".

17.06.05 The August Krogh Institute. CMRC summer competition in scientific presentation.

22.09.05 The August Krogh Institute. "Red blood cell and control of the human circulation".

04.+18.11.05 The August Krogh Institute. CMRC Youngsters arrangement. "Basic statistics for researchers".

07.12.05 The August Krogh Institute. CMRC informal winter "competition" in oral presentation.